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DR. W. G. MACCALLUM, *President*.

THE LESIONS FROM TWO CASES OF BRADYCARDIA ASSOCIATED WITH AURICULAR FIBRILLATION.

ALFRED E. COHN, M.D.

(From the Hospital of the Rockefeller Institute for Medical Research.)

The cases from which the lesions were shown were reported clinically by Dr. James Mackenzie. Dr. Thomas Lewis has also reported the first one.

Lantern slides of the sino-auricular node of the first case at various levels were shown. The node is almost entirely replaced, especially at its lower portion, by connective tissue. The

vessel to the node is apparently normal. Sections of the auriculo-ventricular bundle show an old sclerotic lesion of the main stem shortly after the origin of the bundle, causing a complete transverse lesion. The diagnosis of auricular fibrillation and heart-block had been made on the ground that the ventricular rhythm was regular in the presence of auricular fibrillation. The presence of auricular fibrillation was established by means of electrocardiograms.

Sections of the sino-auricular node of the second case showed a very slight degree of fibrosis. A few small haemorrhages (probably ante-mortem) and one area of round cell infiltration were seen. The auriculo-ventricular bundle in this case was not interrupted.

The absence of the A-wave from the jugular pulse, together with complete ventricular irregularity, made it likely even without electric curves, that the auricles in this case, too, were fibrillating. It was supposed that the A-V bundle was capable of conducting impulses. There were periods when the bradycardia gave place to a relative tachycardia, but the rhythm was always irregular.

The two cases are shown together to bring out the fact that accurate clinical diagnosis in these complicated conditions can be made with certainty. The fact that there was an extensive lesion of the node in one case and a relatively slight lesion in the other renders it unlikely that these lesions are responsible for auricular fibrillation. The transverse lesion of the node in one case and a relatively slight lesion in the other renders it unlikely that these lesions are responsible for auricular fibrillation. The transverse lesion of the A-V bundle in the first case determined the regular rhythm; while the intact bundle in the second made a complete ventricular irregularity possible.

The etiological factor in the first case was syphilis. The patient was also a heavy smoker and drinker. The second case was one of arterio-sclerosis. The patient had been a heavy worker and smoker.

Discussion.

DR. MACCALLUM asked Dr. Cohn if he had any idea of the etiological factors in this condition.

DR. COHN said that the first patient was a syphilitic; he had a number of syphilitic lesions, had had malaria, had a marked degree of arterio-sclerosis. Dr. Cohn thought that all these factors would explain this condition.

HODGKIN'S DISEASE INVOLVING THE UTERUS.

W. E. D. JESSUP, M.D.

This case is reported chiefly because of the unusual involvement of the uterus.

Clinical History: Mrs. W., admitted to New York Skin and Cancer Hospital March 17, 1911. Service of Dr. W. S. Bainbridge. Age 43 years. Birthplace Russia. Family history negative. Does not use alcohol. Has had ten children, last four weeks old. One miscarriage.

Previous Diseases: Chronic rheumatic manifestation during past year.

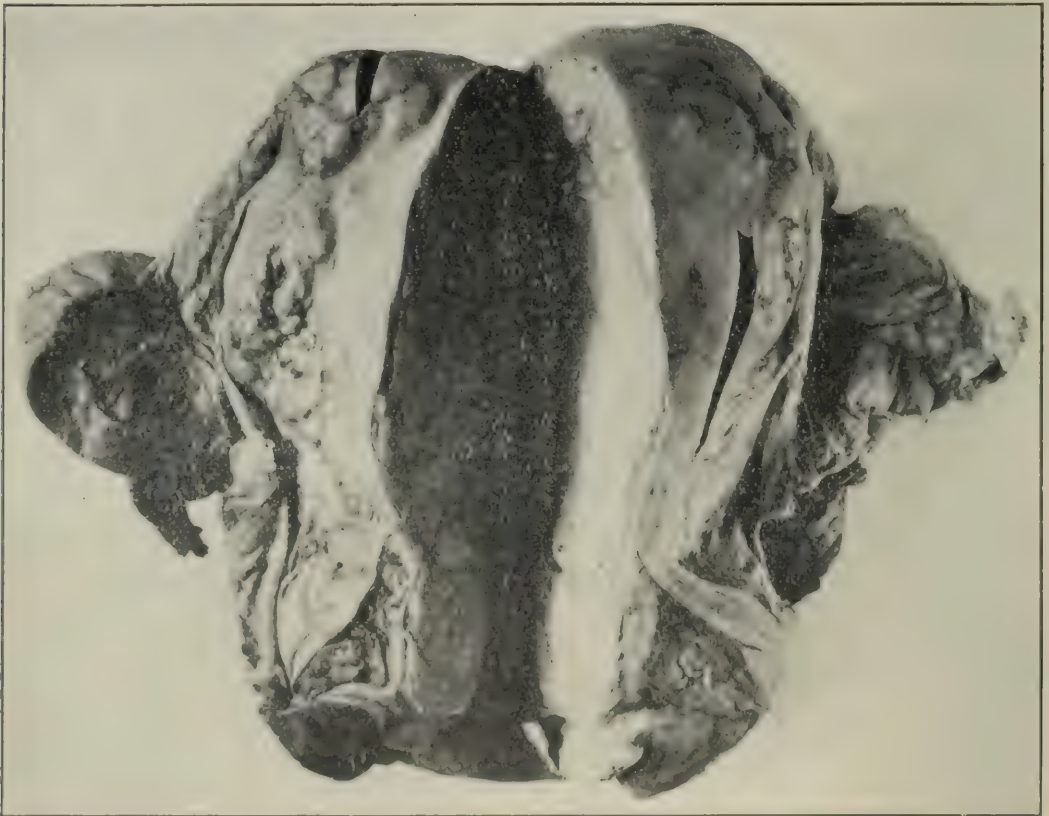
Present Illness began November, 1910, with enlargement of glands of both axillae. Two weeks later glands of right groin enlarged. Then glands of neck, and finally general enlargement of external glands to size of pea or larger.

Physical Examination: Poorly nourished, heart and lungs negative. Glands of neck, axillae and groins enlarged. Neck and breasts greatly swollen and skin over this area tense.

Vaginal examination showed enlarged uterus, and clinical diagnosis of sarcoma of uterus was made with metastases in the lymph nodes. Patient was under observation for three months. Axillary and inguinal nodes were excised for examination. Inguinal nodes, removed in March, showed necrosis. A month later axillary nodes showed typical tubercle tissue with giant cells

(some of these giant cells later showed tubercle bacilli). The great superficial swelling of the upper part of the body was accompanied by itching. Thickening and infection of the skin resulted from the patient's scratching. Sections of this thickened skin showed inflammatory changes, but nothing on which to base a diagnosis of new growth or Hodgkin's.¹

During her stay in the hospital patient suffered from pain in the neck and arms, which continued much swollen. There was

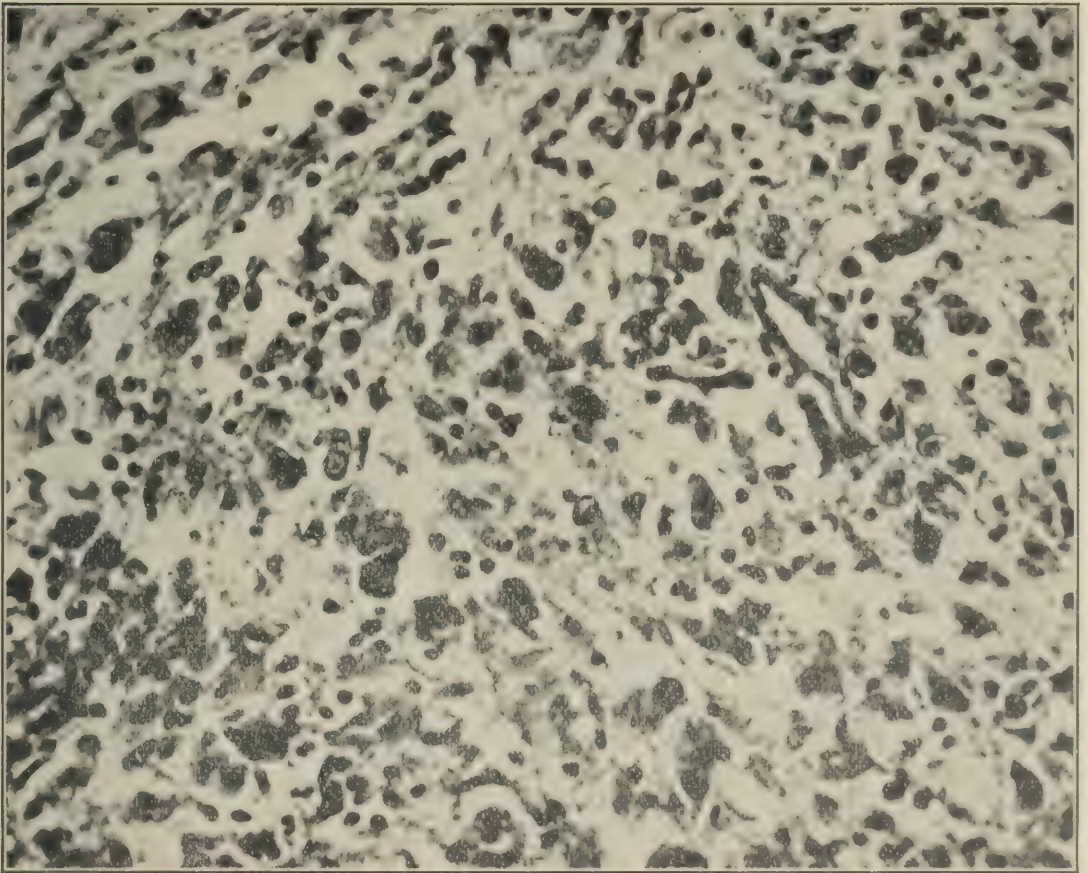


Uterus invaded throughout by Hodgkin's disease. Tubes and one ovary also invaded.

rapid pulse and dyspnoea and periods of marked restlessness, especially at night. The temperature remained normal except for an occasional short rise. Repeated blood examinations showed an increase of polymuclears, the range being 85 to 93 per cent. There was no increase of eosinophiles. Death appeared to be the result of exhaustion.

¹Re-examination of some of these nodes in the light of subsequent diagnosis shows areas suggesting Hodgkin's disease.

Autopsy, by Dr. R. F. Barger, June 25, 1911. Female of about 40; emaciated. Extensive swelling of neck, more so on right side. Rigor mortis not developed. Both axillae and breasts infiltrated with hard nodules; nodules also in groins. Entire body covered with an eruption of spots the size of millet seeds, some crusted, some show complete healing.



Uterine wall near mucosa showing giant cells and endotheloid cells. (x 400)

Thorax: Mediastinal glands enlarged. Left lung collapsed; left pleural cavity filled with bloody fluid. Right lung adherent.

Heart: Normal.

Spleen: Normal size; shows small white nodules.

Kidneys and Pancreas: Normal.

Liver: Congested.

Gall Bladder: Normal.

Iliac lymph nodes enlarged, ranging in size from 1/3 cm.

Mesenteric nodes uniformly enlarged.

Stomach: Normal.

Uterus: Measures 12 cm. in length and is 9 x 6 cm, at fundus. Surface nodular. Entire wall infiltrated with growth of dense fibrous tissue, which has caused apparent destruction of all the muscularis.

Tubes: Show similar nodular thickening at uterine end.

Ovaries: Normal size and fibrous. In one there is an area of growth similar to that in uterus.

Microscopical Examination.

Sections of different parts of the uterus show growth of epithelial cells, small round cells, with scattered giant cells. Portions are densely fibrous in character. The structure of the mucosa is almost entirely lost, only a few scattered glands remaining. One ovary, the Fallopian tubes, the mesenteric, iliac and bronchial lymph nodes, spleen and breasts show similar growths; also the deeper layers of the skin of neck. The smaller nodules, especially those in the spleen, show the large type of cells, with mitoses and very little of the dense fibrous changes seen especially in the uterus and some of the lymph nodes.

Diagnosis.

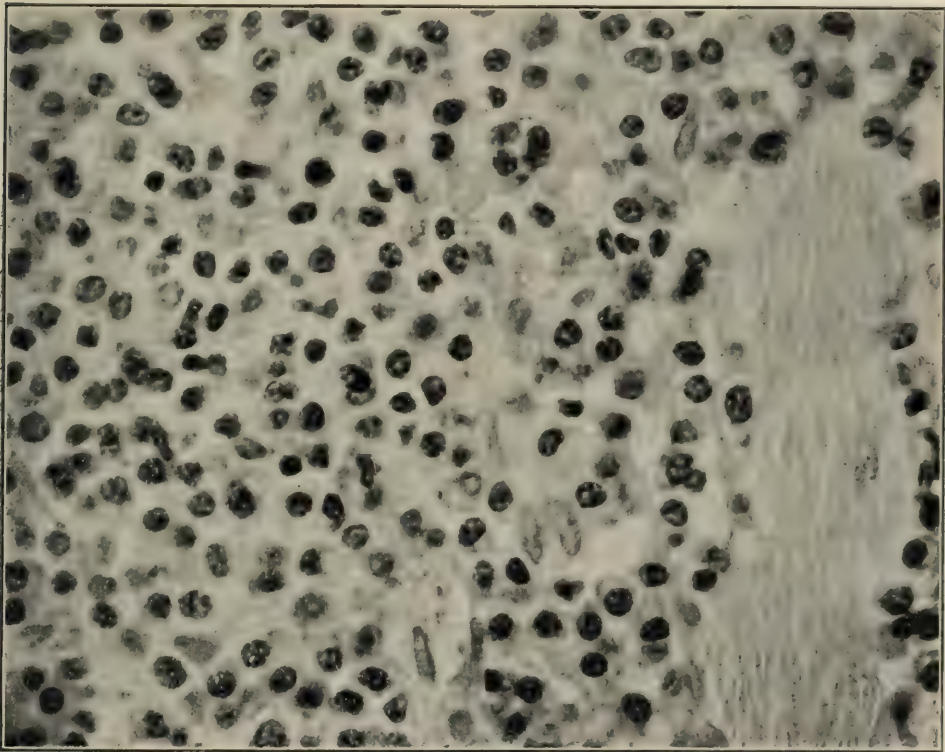
Hodgkin's disease, involving the uterus with tuberculosis of some of the superficial lymph nodes.

PLASMA CELL TUMOR OF THE TONGUE.

For permission to show slides from this case I am indebted to Dr. E. M. Foote, in whose service at the New York Skin and Cancer Hospital the tumor was removed. Some members of this Society have already had an opportunity of examining the tumor, and the patient was shown last March at a meeting of the New York Surgical Society.

Mr. P., 45 years of age. Family history negative. Venereal history negative. Habits: moderate use of tobacco up to four years ago. Typhoid when a child. Muscular rheumatism four years ago.

In 1901 a rectal abscess was incised and drained with three subsequent operations. Final healing four years ago, and then mouth became tender with swelling of lips, cheeks, and gums.



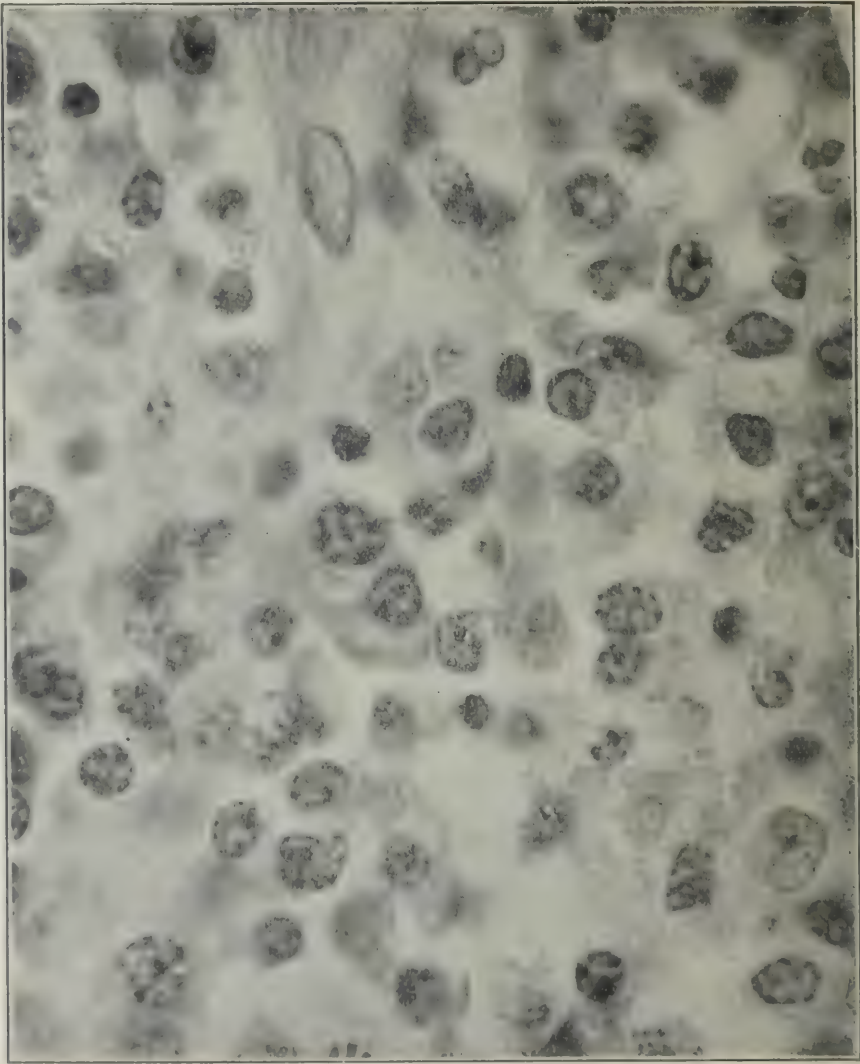
Plasma cells and muscle fibre, high power.

In December, 1909, portions of the lips and cheeks were cut away. In July, 1910, tongue was cauterized twice by Dr. Mayo of Rochester. On admission to hospital, November, 1910, patient complained of enlargement and soreness of tongue.

The Wassermann reaction was negative.

Physical Examination: Heart, lungs, and abdomen negative. Tongue showed on dorsum a swelling $1\frac{1}{2}$ cm. across and along left border a cicatrix 1 cm. wide. These portions were excised and submitted for examination. After patient left hospital,

the tongue continued to enlarge and a second operation, removing tip of tongue, was performed. Subsequently patient developed a cough, and tubercle bacilli were found in sputum. The growth of the tongue appeared to be arrested after the second operation.



Plasma cells (x 1000)

Pathological Examination of Tongue: Macroscopical Examination: (a) Wedge from dorsum of tongue, 3.5 x 2 cm. and 1 cm. thick. Surface has warty appearance. On section, tissue below epithelium is firm, pale, and homogeneous in appearance. (b) Wedge from side of tongue, site of former operation,

5.3 x 1.8 cm. and 1 cm. thick. Center of surface occupied by cicatrix 1 cm. broad. On section, tissue appears like that from dorsum.

Microscopical Examination.

Sections from different parts of both specimens show same character of growth. Beneath the surface epithelium, and extending down and invading the muscular layer, is a growth of large cells with a large oval or round nucleus with abundant chromatin. The growth is diffuse and there is no grouping of the cells in nests, nor do they seem intimately connected with the connective tissue framework. Where the muscle is invaded there is atrophy of the fibers. Levaditi stain for spirochaetae is negative, as is also stain for tubercle bacilli. In the region of the scar there is inflammatory infiltration. Examination of portion of growth from tip of tongue removed at second operation showed similar growth of cells of the plasma-cell type with more congestion and inflammatory infiltration.

Diagnosis.

It seems possible to rule out sarcoma and syphilis and in the absence of giant cells, tubercle tissue and tubercle bacilli diagnosis of tuberculosis does not seem justified. The growth appears to belong to the group of plasma cell tumors which have been described by several observers, and to which the name "plasmoma" or "plasmocytoma" might be applied.

The literature shows reports of a few tumors composed largely of plasma cells; some arising in bone marrow with the characteristics of a malignant tumor, others of apparently benign character. Of the former type two may be cited, published by Hoffman (*Ziegler's Beiträge*, Bd. 35, 1904, p. 317) and Wright (*Jour. Boston Soc. Med. Sci.*, 1900, p. 195). The tumors originated in the marrow and were multiple, with metastases involving the bone in various parts of the body. A somewhat different type is described by Maresch (*Verhandlungen d. deutsch. path.*

Gesellschaft. 13. Tagung. Leipzig, 1909) in a tumor that was removed from the neck which proved to be largely made up of plasma cells. After the death of the patient similar nodules were found in the liver, spleen, and bone marrow.

In the second group belong the cases of Schridde (*Zentralblatt f. all. Path., u. path. Anat.*, Bd. 16, 1905, p. 433), and Bolt (*Frank. Zeits. f. Path.*, Bd. 1, 1907, p. 172). Schridde's case was from the nose and was first thought to be a rhinoscleroma, but both the bacilli and Mikulicz cells were absent. Bolt's case came from the naso-pharynx, and was a tumor about $1\frac{1}{2}$ cm. in diameter. The tumor did not recur after excision. The case of Werdt (*Frank. Zeits. f. Path.*, vi, 1911, p. 180) was a movable tumor of the naso-pharynx, pushing forward the uvula, and about 2 cm. in diameter. The mass had an uneven lobular surface and was of a bluish-red color. No recurrence was noted some months after operation. Microscopically it was composed of closely packed plasma cells, with a scanty fibrillar stroma. Hedinger (*Frank. Zeits. f. Path.*, vii, 1911, p. 343) describes a tumor measuring 8×20 mm., arising in connection with long standing adenocarcinoma of the sweat glands of the scalp. The tumor was formed almost entirely of hydropic plasma cells. At first glance it resembled a large-celled sarcoma with transition areas into granulation tissue; but on staining the cells by special methods they showed the morphology of true plasma cells lying in a meshwork of delicate connective tissue. The regionary lymph nodes were invaded by the adenocarcinoma, but no metastases had been formed by the plasma cells. The mass must be considered not as a true tumor but as an inflammatory new growth, there having been a recurring inflammation about the carcinoma of the scalp.

This tumor of the tongue would appear to belong to the second group of benign plasma cell tumors.

Discussion.

DR. LEVIN: I should like to ask Dr. Jessup from what part of the tongue the piece of which the photograph is shown here

was taken. If I understand the case correctly, there are a number of ulcerations around the tongue, and the tongue is enlarged; but what is not clear to me is where that part is situated which served for the microscopical study. If one should judge from the appearance of the tongue, the question arises whether the condition is not an inflammatory one. I have recently seen a tongue very similar to the one presented here, which, after a few weeks of treatment with mild antiseptic applications, became normal.

DR. MACCALLUM felt that the assumption of Wright and Hoffman and others of the plasma cell nature of the elements of certain tumors which they have described should be received with some hesitation, because plasma cells are in their very nature independent wandering cells, and it would be like speaking of a tumor composed of polymorphonuclear leucocytes. If these are plasma cells, it seems necessary to consider the possible inflammatory nature of the lesion which Dr. Jessup describes.

DR. EWING: I should like to ask the doctor if he is satisfied that he can explain the tuberculous infection of the lymph nodes in one portion of the lymphatic system, as a secondary infection.

In regard to the second case, I was much interested to see that case turn up at this time, as I spent a good many hours working and worrying over it; the material was sent to me two or three times. I agree with Dr. Jessup in the main conclusion that he makes that we have to deal with a tumor, or tumor-like process, in which the cellular elements resemble plasma cells, and that is about all that can be said. I fail to find anything in the literature which accords with this condition. When I heard a few weeks ago that tubercle bacilli had been found in this patient's sputum, I felt that that was an additional factor which might explain the condition of the tongue, and I am disappointed to find that Dr. Jessup is not inclined to associate this condition with a tuberculous process in the lung.

I did not at any time believe the process was a true sarcoma, although it came into my hands with a diagnosis of sarcoma from several sources. To me the process is extremely interesting and

quite obscure, and while I agree with the diagnosis in general that Dr. Jessup has given, I do not think the condition has anything to do with the ordinary myeloma.

DR. JESSUP: In reply to Dr. Ewing's question in regard to the glands: These glands, as I said, were examined during the life of the patient on two or three occasions, and the only definite thing found was the tuberculosis. There were some glands which were very fibrous and tough, and looking through them now in the light of the subsequent diagnosis, there are areas from which I think the diagnosis of Hodgkin's could be made. Of course, I assume that the tuberculosis was a secondary development. It was certainly present at the time the patient came to the hospital.

With regard to the question about the part of the tongue from which this photograph section was removed, of the two specimens passed around, the one with the smooth surface was the portion that was operated upon and that central elevation was the portion sectioned for this photograph. Subsequent operation from the tip of the tongue showed a similar condition.

With regard to Dr. MacCallum's question about other cases of Hodgkin's, I have not had time to look through all the literature. I have looked through Kurt Ziegler's recent monograph, and he has reported a number of cases in which he has found Hodgkin's in the ovaries and also in the testicles, but I could find no case involving the uterus.

THE VALUE OF ABSORPTION METHODS IN THE WASSERMANN TEST.

MIRIAM P. OLMSTEAD.

(From the Department of Health, Research Laboratory, New York City.)

A series of comparative Wassermann tests has recently been made to determine the value of Rossi's and Wechselsmann's methods of absorbing from the serum to be tested for syphilitic antibodies, certain components that interfere with a positive reaction.

Natural anti-sheep amboceptor is frequently present in human serum, so that on the addition of two units of amboceptor in the course of the Wassermann test there is an excess of amboceptor and hemolysis is unduly increased. Rossi¹ has described a method of absorbing the natural amboceptor from the serum previous to the test, thus insuring the balance of the hemolytic system and increasing the delicacy of the reaction of the Bauer modification,² which depends for at least part of the hemolytic action on the natural amboceptor content of the serum. As this is an unknown quantity, varying from zero to twenty or more units, there is no certainty of the hemolytic system being in balance, and the accuracy of the reaction cannot be depended upon.

The presence of natural anti-sheep amboceptor in the serum is first determined by incubating for one hour in the water-bath at 37° C. two parts of inactive serum, two units of complement, one part of 5 per cent. sheep cell suspension and twenty-eight parts of physiological salt solution. Hemolysis, partial or complete, indicates the presence of anti-sheep amboceptor, which, according to Rossi, may be removed as follows:

Three parts of inactive serum and one part of washed packed sheep cells are mixed, kept on ice for from twenty to thirty minutes, and then quickly centrifugated. The serum that is drawn off is tested as usual.

Out of eighty-eight sera tested by us for amboceptor, forty-four, or 50 per cent., gave evidence of the presence of natural anti-sheep amboceptor; and these same sera tested after absorption had no hemolytic action on sheep cells, indicating that absorption had taken place.

A comparison of Wassermann tests on absorbed and untreated specimens verifies Rossi's assertion that an excess of amboceptor interferes with a positive reaction in the diagnosis of syphilis. Of forty-seven specimens that gave a negative reaction in the regular Wassermann test, five, 10.6 per cent., were positive after absorption. Two were from undoubtedly specific cases and both of these gave a positive reaction after absorption. Eleven had a past history of syphilis, but

no present symptoms; of these one gave a positive reaction after the absorption. Of the twenty-nine cases with a suspicious history, two gave a positive reaction after absorption. Five cases with no luetic history remained negative after absorption. Experience has shown that if the cells used in absorption are not thoroughly packed the serum is so diluted that it reacts no more strongly than in the unmodified test. Our tests give no indication of any danger of false positive reactions through the use of Rossi's method.

Wechselmann³ called attention to the presence in heated serum of complementoids, which, though they have no hemolytic action, retain haptophore groups, hence are capable of being bound by the antigen-antibody combination and prevent the latter from binding complement, which is thus left free to hemolyse the cells subsequently added.

Noguchi⁴ and others have expressed doubt as to the complementoid nature of the serum components thus preventing a positive reaction, but agree that the accuracy of the test is increased by their absorption.

Wechselmann recommends treating all sera to be tested for syphilis with barium sulfate, which has the power of absorbing complementoids and hence increases the binding of complement. The technique of the absorption is as follows:

Nine parts of inactive serum, thirty parts of physiological salt solution and five parts of a 7 per cent. suspension of freshly precipitated barium sulphate are shaken together, incubated for an hour at 37° C. and centrifugated. Of the supernatant fluid, ten times the regular amount for the Wassermann test must be used.

We have treated in this way forty-three specimens that had given a negative reaction in the unmodified Wassermann test, six of which—a percentage of 13.9—gave a positive reaction after absorption. Five specimens from which a history of syphilis could be absolutely excluded were even more clearly negative after treatment with barium sulfate than before. Seven positive sera have been treated with barium sulfate and have not thereby

lost any binding power. That barium sulfate itself has no binding power has been controlled in each set of tests by a treated negative serum or by barium sulfate and salt solution alone.

Eight specimens with a suspicious gonorrheal history that had given a negative reaction in the unmodified complement-fixation test for gonorrheal antibodies were treated with barium sulfate, after which two of them reacted positively, suggesting that Wechselmann's absorption method might be of as much value in the serum diagnosis of gonorrhea as of syphilis.

At Dr. McNeil's suggestion a combination of the Rossi and Wechselmann methods was tried, in order to absorb the natural amboceptor as well as the other serum components that interfere with a positive reaction. Sixty-six specimens that had given a negative reaction in the unmodified test were treated first with sheep cells and then with barium sulfate; eighteen of these, 27.2 per cent., were positive after absorption.

Exactly the same percentage was obtained in similar tests for gonorrheal antibodies, three out of eleven negative specimens being made positive by absorption with sheep cells and barium sulfate.

Wolff⁵ has emphasized the value of the barium sulfate treatment for the absorption of complement as well as complementoid; and he advises the use of active rather than inactive serum, as heating at 56° C. destroys some antibodies, thus weakening a positive reaction.

We have treated with barium sulfate twenty-eight negative specimens of active serum. Nine of these, 32.1 per cent., gave a positive reaction after absorption. Although this percentage is higher than in the series of tests with inactive serum from which both natural amboceptor and complementoids had been absorbed, the use of active serum does not seem to be advisable. Three specimens from which a history of syphilis⁶ could be absolutely excluded gave a positive reaction and in at least one other instance it seemed highly probable that the binding was non-specific.⁷ In a number of instances (eleven) one-tenth c.c. of serum bound more strongly than two-tenths. Though this phenomenon has

not been constant, it has occurred so frequently as to render the test unreliable.

Wechselmann, Wolff and others have emphasized the non-suitability of commercial barium sulfate for absorption purposes; but they have not stated how fresh a precipitate should be used. We have found a precipitate four weeks old as effective as a perfectly fresh one. Since, however, a suspension is apt to become anticomplementary in three or four weeks it is advisable to use a fresh suspension about every two weeks. A simple method of precipitating barium sulfate is described by Wolff.¹

Mix fifteen c.c. of 5 per cent. sodium sulfate and 10 c.c. of 5 per cent. barium chloride. Centrifugate after precipitation has taken place, draw off the supernatant fluid and wash the residue, barium sulfate, once in physiological salt solution. After centrifugalization suspend the barium sulfate sediment in 25 c.c. of physiological salt solution, which makes the proper dilution for use in absorption.

Summary: Thus it appears that by absorption methods the number of positive reactions in the Wassermann test for syphilis is increased. The relative value of the Rossi, Wechselmann and Wolff methods of absorption is indicated by the following comparison of the various tests just described:

By the absorption of natural amboceptor by sheep cells 10.6 per cent. of the negative specimens were made positive.

By the treatment of inactive serum with barium sulfate 13.9 per cent. of the negative specimens were made positive.

By the use of both sheep cells and barium sulfate on inactive serum, 27.2 per cent. of the negative specimens were made positive.

By the treatment of active serum with barium sulfate 32.1 per cent. of the negative specimens were made positive.

Wolff's method of treating active serum with barium sulfate gives the highest percentage but is not, according to our experience, reliable.

The combination of Rossi's and Wechselmann's methods gives a high percentage; and so far as may be judged from the

results of our few tests, there is no danger of thereby rendering the Wassermann reaction over sensitive. The effect of barium sulfate on sera free from syphilitic and gonorrhoeal antibodies should, however, be tested at length before the use of barium sulfate in the routine serum diagnosis of venereal diseases is recommended.

Rossi's method of absorbing natural amboceptor from the serum to be tested is of practical value and perfectly safe.

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- ²*Deut. Med. Wochenschr.*, 1908, Bd. 34, p. 698.
- ³*Zeitschr. f. Immunitätsf.*, 1909, Bd. 3, p. 525.
- ⁴*Jour. Exp. Med.*, 1911, Vol. 13, p. 217.
- ⁵*Zeitschr. f. Immunitätsf.*, 1911, Bd. 11, p. 154.
- ⁶*Zeitschr. f. Immunitätsf.*, 1911, Bd. 11, p. 154.
- ⁷*Jacobaeus had a similar experience.*
- ⁸*Zeitschr. f. Immunitätsf.*, 1911, Bd. 8, p. 615.

SIGNIFICANCE OF THE GROUP OF "HEMOPHILIC" BACILLI IN CONJUNCTIVITIS, ESPECIALLY IN THAT OF "TRACHOMA."

ANNA WESSELS WILLIAMS.

(From the Division of Laboratories, Department of Health, New York City.
Director, William H. Park, M.D.)

During the past year and a half ten workers have been grouped in the Health Department for the purpose of studying trachoma and allied conditions from all standpoints, but especially from that of the public school children of New York City. These workers have been advised and encouraged most helpfully by Dr. Wm. H. Park, Director of Laboratories. The paper tonight is a report of one phase of the work—a part of the bacteriologic study—and it will emphasize only two points.

From the important papers of Dr. Noguchi and Dr. Cohen¹⁻² read before this Society in 1910-11, we have had a good opportunity of learning of some of the recent work that has been done on the etiology of trachoma; how certain epithelial cell inclusions, which have been found in large numbers in the acute papillary stages of the disease, are considered by the majority of the many students of this subject to be the cause of trachoma. Noguchi and Cohen believe that these inclusions are an accompanying infection; Wolbach, McKee³, Addario⁴ and a very few others think they are degeneration products of the epithelial cell; while Hertzog⁵ and a few others think they are involution forms of the gonococcus.

From time to time in the history of trachoma investigations the claim that the gonococcus is an etiologic factor in trachoma has been urged. In order to find out whether or not the gonococcus had anything to do with the trachomatous eyes of school children, and at the same time to make a more comprehensive bacteriologic study of these eyes and to continue the investigations of the trachoma inclusions started by C. R. Gurley and J. Chase in our laboratory in 1910 this part of the study was planned. An eye clinic was established in the Research Laboratory, with Dr. Wootton, the Department's Ophthalmologist, in charge, assisted by Dr. Von Sholly, Miss Gurley and others of the group.

A history and a minute record of the course of each case has been kept by the folder and card index system. All of the charts and chart holders for the work as well as a certain amount of money for the carfare of those children living at a distance and too poor to pay were presented by the Committee on the Prevention of Blindness of the Sage Foundation. These aids were most helpful to us in getting quickly and satisfactorily into the work.

Following the course for so long a time of such a large series of cases of all types of conjunctivitis by full written records has seldom, if ever, been done before. It has allowed us to make the column of recovering cases seen in Table 1 and to

trace a certain number of cases from acute catarrh through a series of attacks to papillary trachoma with typical inclusions. Tables showing the course of the cases will be given in the full report at a later date. We mean to keep track of the cases of trachoma which we have recorded as cured with the exception of mild folliculoses, in order to determine if possible whether subsequent symptoms of trachoma are the result of an exacerbation or a reinfection.

In our clinic after the minute description of the eye condition was recorded, in each new case, and from time to time in some of the older cases, a light curettage of the palpebral conjunctivae was made, then a sterile cotton swab was rubbed over the curetted areas and was placed immediately into a tube of ascitic-broth which was taken at once to the laboratory, where part of it was planted on a series of culture media plates, including glucose-ascitic agar, blood agar and plain alkaline veal agar. All were then placed in the incubator at 36° C., and were examined within 24 hours, and later when necessary.

From one case among the first growth, Miss Wilson found a few gonococcus-like colonies on glucose-ascitic agar and on blood agar. These were fished and were found to be a tiny gram negative bacillus which was strictly hemoglobinophilic. Since then, rabbit blood broth, instead of ascitic-broth has been used for the cultures taken directly from the eye, since this medium is better for the tiny bacillus and equally good for the gonococcus. The blood broth acts as an enriching medium in those instances—and they are not few—where there is no growth on the original plates. After about 24 hours in the incubator the blood broth in practically all the acute papillary trachoma cases (Table I) has shown an abundant growth of the little bacillus, and blood agar plates made at this time from the blood broth culture generally have given many typical colonies. This tiny bacillus in blood broth grows in small and large compact groups which, after Gram, counterstained by fuchsin, appear under the low power as small granular masses taking a brilliant red stain. The individual bacillus does not show so brilliant a stain. Stained by

Giemsa these small groups of bacilli have morphology and staining characteristics very similar to those of some of the trachoma inclusions. Our attention was thus early directed to the question of the identity of the two. I shall speak of this a little later.

In looking up the literature on hemoglobinophilic bacilli found in eye diseases (Table II), I was surprised to find that most investigators say that the influenza bacillus is found rather infrequently—with the exception of Müller's series of cases; and that the Koch-Weeks bacillus is found practically only in acute conjunctivitis—and that it grows better on serum agar than on blood agar. Müller⁶ found in a large percentage of his acute trachoma cases in Egypt a tiny bacillus which he could not differentiate from the influenza bacillus, though he thought it was another species, since there were no cases of influenza about.

In Manila recently Edwards⁷ found in a few cases of trachoma a minute Gram-negative bacillus which was a strict hemoglobinophilic. He called it *B. trachus*, and suggested that it might produce the trachoma inclusions.

A few authors—Kamen⁸ and others, claim that the Koch-Weeks bacillus is a strict hemoglobinophilic and that the cultural work of those who claim otherwise is open to criticism.

So we had first before us the problem of the relationship of our bacillus to the influenza and the Koch-Weeks bacillus.

After carefully examining a series of clinically typical "pink eye" and getting an abundant, practically pure growth of a bacillus similar in general to the one we were isolating from our papillary trachoma cases, we were forced to the conclusion that those who consider the Koch-Weeks bacillus a strict hemoglobinophilic are correct. The word hemophilic, therefore, in Table II and in the title of this paper should be changed to hemoglobinophilic. Furthermore, in this series of cases of "pink eye" we found that the size of the bacillus in the direct smear of the exudate varied from coccus forms to comparatively long forms, while the pure cultures did not always vary correspondingly, hence we cannot consider the point of size in the direct smear of worth in differentiating Koch-Weeks and the influenza bacillus

(see Table II). It was surprising to us to find in the direct smear from several of the cases of "pink eye" so few distinct bacilli, although the culture plates showed an abundant growth. In these smears and in the direct smears from our trachoma and follicular conjunctivitis cases where the tiny bacillus was almost invariably found, no recognizable bacilli were seen within the leucocytes, while we found the groups lying within the cells for the most part scattered and atypical—corresponding frequently to Lindner's⁹ extra cellular "initial bodies," found in his cases of trachoma.

It has been stated that trachoma gives no constant bacteriologic findings. In order to get further evidence on this point, that is, to find whether or not the tiny bacillus we were finding so constantly in our cases of papillary trachoma were present in the cases direct from other countries, we are examining at Ellis Island, through the kindness of Dr. Stoner, Chief Medical Officer, and of his assistants, cases of typical and doubtful trachoma in the immigrants. We have already examined 16 cases, in three of which with marked papillary trachoma both hemoglobinophilic bacilli and trachoma inclusions were found. In four border line cases and two follicular conjunctivitis cases only bacilli were found, while in seven recovering cases no bacilli were found, and only a few inclusions in three of these. Thus, so far, these findings correspond with those of our school children.

We have isolated, in all, 128 strains of a hemoglobinophilic bacillus from our series of 213 cases (Table II), and we have as yet not been able to find any distinct differential points between any of them or between our strains and those of the *B. influenzae* as described by others or as studied by us. Two strains of the *B. influenzae* kindly sent us by Dr. Wollstein have been studied with our cultures.

It is true that certain of our strains show small peculiarities which seem to be holding through many culture generations, such as greater tendency to thread formation, more marked pleomorphism, large or small size, etc.; but so far we have found no

distinct relationship between these characteristics and the clinical picture.

We are compelled, therefore, for the present to group all of these bacilli with the influenza bacillus.

Dr. MacNeal and Dr. Povitzky are studying complement deviation of the group, but so far have encountered little but difficulties.

Miss Mishulow is getting some interesting results with symbiosis studies, but at present they can only be used practically to show some of the difficulties in the way of demonstrating and of isolating the little bacillus. Staphylococci seem to have a decidedly inhibitory action on the growth, especially in blood broth, while certain non-hemolysing streptococci favor the growth slightly, and the xerosis group shows a markedly favorable action. On non-blood media, growth has been obtained only with the xerosis bacillus.

The fact that the staphylococcus inhibits growth may account in part for negative results in some of our apparently recovering cases where staphylococci were in abundance.

I said that early pure cultures show a resemblance to some trachoma inclusions. These early cultures show many forms similar to Lindner's initial bodies and smears taken daily from the same culture and stained by Giemsa show morphologically a similar cycle of development to that described by Prowazek and others, especially by Lindner¹⁰ in 1910, for the famed chlamydozoa of trachoma or the trachoma inclusions. In other words, in the culture of the tiny hemoglobinophilic bacillus we have, morphologically, a culture of the trachoma inclusions. Thus we have, first tiny coccus-like or short bacillar bodies taking a clear blue stain, and later the appearance of very tiny metachromatic granules within these blue bodies, then the gradual disappearance of the blue bodies leaving a mass of metachromatic granules. I have placed under the microscopes some initial inclusions and a more developed included form from a case of papillary trachoma, also smears of a culture from the same case made after 2, 3 and 5 days' growth on blood agar, and you can

readily see for yourselves the striking resemblance between the two, a resemblance still more striking when many smears and cultures are examined.

That the epithelial cells of the conjunctiva may take up bacteria is a well-known fact, but nobody before has, to my knowledge, followed the cycle of development of the bacteria within the cells, and no one has recognized the possibility of any of the groups of hemoglobinophilic bacilli found by us so frequently in trachoma having the power to grow in the epithelial cells, except Edwards, who merely suggested that the bacilli which he found might produce the trachoma inclusions.

In most cases of blenorrhoea, gonococci are found in the conjunctival epithelial cells, and since these organisms in pure cultures pass through a cycle of development somewhat similar to that of the hemoglobinophilic bacillus, that is, the production ultimately of masses of metachromatic granules in the cultures, with the gradual disappearance of the blue-staining organisms, there is reason to suppose that they, too, may form inclusions, especially in certain cases, although this is a subject which needs much further study in connection with a bacteriologic study of gonorrhoeic and non-gonorrhoeic ophthalmia neonatorum.

In none of our school children cases so far have we found gonococci. While the two facts which we wish to emphasize in this paper, namely, first, the finding of our tiny bacillus so uniformly in our cases of papillary trachoma, where we have found, too, the trachoma inclusions, and second, their morphologic similarity, lead us to conclude that bacillus and inclusions are probably identical in papillary trachoma, and hence that the bacillus is probably the cause of the disease.

The hypothesis that one or more of the group of hemoglobinophilic bacilli is the cause of trachoma explains many other hitherto unexplainable phenomena of this disease, (1) its regular onset; (2) its insidious course; (3) its variable contagiousness, with its exacerbation of secretion; (4) the continued presence of trachoma in certain districts where helping causes are present, etc. Of course, suitable monkey inoculations would in all prob-

ability be all that is necessary for proof or disproof. It is, to say the least, a very good working hypothesis. For it means practically that all cases of secreting conjunctivitis, however mild, should be looked after until all secretion has ceased. With organisms of this type which presumably may lose their virulence quickly, sufficient oversight of cases gives great hope of getting rid of dangerous carriers. On the strength of these results we are strongly advocating and trying to get established special mixed classes for the school children who are now being sent to school with very slight secretions while receiving treatment at clinics. The Board of Education has the plans under consideration. We are also advocating more minute home inspection and instruction, and we are hoping for help in this part of the work from organizations whose work lies in these directions.

To lessen the disease among our immigrants, our immediate hope is the establishment by the ship companies of more prophylactic measures on board ship. With arrangements for the isolating of *all* secreting eye cases, and the helping to keep *all* eyes clean by boric acid solutions, etc., the Immigration Bureau at Ellis Island would in all probability not need to deport, as they do now from time to time, a whole group of cases of acute papillary trachoma.

With these measures established, if our hypothesis is correct, we can hope in a reasonable time to have trachoma under control, if not practically stamped out.

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TABLE II.
Showing several Points in Group of "Hemophilic" Bacilli as noted in Published Reports.

NAMES	WHERE FOUND						DIFFERENTIAL POINTS		
	Human Beings						Lower Animals. Gen. Urin	Size	Hemo- globin
	Eye	Ear	Respi- ratory Tract	Menin- ges	Gen. Urin Tract	Other Loca- tions			
B. influenzae (Pfeiffer)	+	+	+	+	+	+		Short	+
B. of Müller	+							Short	
B. of Koch-Weeks	+		+					Longer	— +
B. trachus (Edwards)	+							Short	+
B. of Davis					+			Short	+
B. hemoglobinophilis, canis (Friedberger)							+	Short	+
Hemoglobinophilic bacilli in author's series of cases	+		+		+			Short Longer	+
Trachoma Inclusions	+				+			Small Longer	+

TABLE III.

Showing Frequency of Hemoglobinophilic Bacilli in Author's Series of Cases.

Diagnosis	Number of Cases Examined	Number of Cases Showing Bacilli
Acute Conjunctivitis ("Pink Eye," etc)	47	38
"Trachoma" {	Acute Papillary Conjunctivitis	46
	Old and Recovering Cases. . . .	13
Follicular Conjunctivitis.	40	31
Folliculosis.	11	0
Total	213	128

Discussion.

DR. WOOTON: Dr. Williams' classification, approached from the clinical standpoint, amounts to about this: Those cases that she has classified as papillary conjunctivitis exhibit hypertrophied conjunctivæ, the blood vessels are either partially or completely obscured, and if follicles be discernible the interstices between them are obliterated by the hypertrophy.

In her cases of folliculosis there is merely a formation of follicles without hypertrophy, and her cases of follicular conjunctivitis are clinically folliculosis with secretion added. The cicatricial forms of trachoma are too well known to require description.

Now, in regard to the cases of papillary conjunctivitis we have followed a good many of them at the Research Laboratory, occurring in school children, and it has been a question whether they ever go on to cicatrization and pannus. I have, however, seen pannus follow in two cases. In these cases of papillary conjunctivitis the trachoma bodies of Halberstaedter and Prowazek are found practically without exception, and we may consider them from the point of view of one or the other of two theories.

The theory advanced by Cohen and Noguchi is that the trachoma bodies do not necessarily imply trachoma at all, but that they are characteristic of an independent conjunctival infection which may become ingrafted on other conditions. If, on the other hand, we start with Dr. Williams' hypothesis, that these various stages of conjunctival affection are different stages of the same disease, caused by repeated infections, possibly with a hemoglobinophilic bacillus which in a certain stage of its development is related to the trachoma bodies, then we must regard these cases of papillary conjunctivitis in children as one of the stages of trachoma.

Dr. Williams' theory certainly explains the tendency of the disease to extend itself in overcrowded communities. Trachoma is not a disease that belongs to any country or to any race, but sometimes to different races in different countries, and always under such circumstances does it afflict those who are overcrowded and live under conditions which render repeated infections likely to take place.

The cases that I have studied at the Research Laboratory have mostly occurred in children. In the adult cases the character of the papillary hypertrophy is in my opinion somewhat different.

RECENT VIEWS ON INFLAMMATION OF THE ENDOMETRIUM AND "ENDOMETRITIS."

ROBERT T. FRANK.

Formerly every seeming glandular increase was classified as "hypertrophic or hyperplastic glandular endometritis." No correspondence between clinical types and pathological findings could be drawn. In the last few years our knowledge has been greatly increased by new investigations. Unfortunately these newer findings have been scarcely heeded in the United States.

Hitschmann and Adler in 1908 reported upon the changes which occur in the normal human endometrium under the influence of the ovary. As described by them, a regular monthly cycle, divisible into four phases, could be observed. (1) The *premenstrual stage* (stage of secretion) is characterized by marked glandular activity, increase in size of glands, enlargement of cells distended with secretion, pseudopapillary formations, and decidual stroma changes. (2) *Menstruation* is accompanied by rapid deturgescence, with extrusion of red blood cells into the stroma and later into the uterine lumen. The gland cells pour out their secretion and rapidly assume simple shapes. (3) The *postmenstrual stage* (stage of rest) corresponds to what formerly was called normal endometrium—simple glands, spindle and round celled stroma. (4) The *Interval* is marked by growth of all constituents. The glands enlarge, saw-tooth forms, high columnar epithelium, mitoses; the stroma shows the beginning of decidual changes and mitotic changes.

Hitschmann and Adler considered the hitherto described glandular forms of "endometritis" as normal premenstrual changes. They limited the term "endometritis" to interstitial forms and considered as sole criteria of inflammation the presence of plasma cells.

The large number of subsequent investigators accept the findings of Hitschmann and Adler with great reserve. All acknowledge that cyclical changes take place, but the consensus of opinion is that no rigid schema can be drawn up. Furthermore, future investigation has shown that, though the presence of plasma cells is a sure sign of inflammation, these cells disappear long before inflammation ceases, and that, therefore, the absence of plasma cells is no guarantee that no inflammation exists.

The main question now resolves itself into whether we can recognize the usual signs of inflammation—exudative, vascular and stroma changes—in spite of the constant cyclical variations, which tend to mask them, and whether true inflammatory affections of the endometrium influence the clinical course. Authors who have attempted to furnish descriptions of pathognomonic

changes (for instance Albrecht and Logothetopoulos) offer no criteria which are convincing. Others, who interpret exaggerated or irregular phases, as due to disturbed ovarian function, are able to correlate the morphological and clinical data to better advantage (Beuttner).

From the evidence at hand it appears certain that minor and moderate changes in the composition of the endometrium—hitherto classified as “endometritis”—are accounted for by cyclical changes; that plasma cells, when present, are a sure sign of inflammation, but that their absence does not make certain the absence of inflammation; that such evidence of inflammation as can be noted elsewhere in the body is frequently masked by the cyclical changes; that when inflammation is actually present (as shown by plasma cells), there may be no clinical signs of “endometritis,” and, on the other hand, that when all the signs of “endometritis” occur no morphological evidence of inflammation may be noted.

On the other hand, all changes, both morphological and clinical, can be accounted for by purely ovarian disturbances which escape anatomical observation, but may be studied by physiological methods—castration, X-Ray of ovaries.

At the present time it is more important to offer a simple and reliable guide to the pathologist for use in making his report on curettings, etc., than to take any fixed and irreconcilable stand in regard to a mooted question. The following plan is offered for use in making reports.

- I. (1) A *premenstrual* or *secretory* stage.
- (2) A stage of *menstruation* (it will be found that mucosae from cases of menorrhagia and metrorrhagia alike conform to this type), and
- (3) an *interval* or *stage of comparative rest*.

Curettings of these types should be reported as “normal endometrium,” with mention of the appropriate stage, regardless of whether the stage conforms accurately with the date of menstruation.

II. If, in addition, plasma cells are found, it is sufficient to

report "endometrium, showing chronic inflammation" and "cyclical stage 1, 2 or 3," as the case may be.

III. Borderline cases between physiological and pathological growth can be classified as "endometrium with exaggerated phase," in order to emphasize the fact that the change is purely secondary (ovarian influence).

IV. Marked glandular cystic hyperplasia, hyperplasia after the menopause, etc., can be reported as such without the use of the word "endometritis."

TWO CASES OF INFECTION WITH LAMBLIA INTES- TINALIS.*

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The *Lambli* Intestinalis or *Megastoma Entericum* seems to be a fairly common parasite in Europe, but in America it has been reported only three times. Lambl¹ found the organism first and called it *Cercomonas Intestinalis*. Later Grassi² and others in Italy found that it was not an unusual parasite in cases of intestinal trouble. Moritz and Hölzl³ made an extensive study of the subject and found the organisms in the stools of half a dozen patients suffering from diarrhoea and in the duodenums of ten tubercular patients who came to autopsy. Paul Cohnheim⁴, in Berlin, reports the parasites in the stomach contents of several cases of carcinoma ventriculi and in the stools of five patients with diarrhoea and also in three normal individuals.

*Since this report was read before the Society, *Lambli* cysts have been found by Mr. John E. Ray, Jr., a senior student of the Cornell University Medical College, in the feces of a baby four months old. The writers have also found them in a boy seven years old who has suffered from diarrhoea. Ht R. B. C. are 4,500,000; Haemoglobin, 82 per cent.

About a dozen other writers have reported cases from Italy, Germany, Russia and Sweden. Stiles⁵, ten years ago, reported the first American case, a patient of Dr. Hemmeter in Baltimore. Emerson⁶ has described in his text book a case from the wards of the Johns Hopkins Hospital. Allen⁷ has recently found the *Lambli*a in a negro girl with diarrhoea who has never been out of Charlotte, N. C. The organism has also been found in mice, rats, rabbits, cats, dogs and sheep, and is probably transmitted to man through dust or food contaminated by the excreta of these animals.

The *Lambli*a belongs to the family of Flagellata and shows four pairs of flagellae. The motile form of the parasite is kite shaped and measures 10-21 m. in length and 5-12 m. in breadth. There is a curious sucker-like mouth which is kidney shaped when seen from the front and concave when seen from the side. The nucleus is divided into two oval bodies which are sometimes united by a bridge. The flagellae causes a rapid, aimless motion sometimes making the organism turn over and over as it crosses the field of vision.

Apparently the motile forms occur in great numbers in the duodenum where they attach themselves to the mucosa by means of their sucker-like mouths. When carried from the duodenum into the lower intestine, they become encysted unless they are hurried along by catharsis or diarrhoea. Under the microscope the process of encysting can be readily observed. The cysts are oval, slightly refractile and measure 10 x 7 m. Sometimes they appear structureless, but more often one can see lines indicating former flagellae or oval bodies indicating the halves of the nucleus.

While the *Lambli*a has been found in normal individuals, it has much more often been found in children and adults suffering from chronic intestinal indigestion. Most observers consider it harmless, but others are inclined to believe that it can start or keep up the condition. Some believe that the parasites, which are often present in enormous numbers, can cover so much mucous membrane as to interfere with the absorption of foods.

It seems to be rather difficult to get rid of the *Lamblia*. Those who have made persistent attempts have found that calomel in small doses is almost the only cure. In some cases the infection lasts for years.

America has so many immigrants from countries infected with the *Lamblia* that one would expect to find it often in our hospitals. While it is an easy parasite to overlook in an ordinary routine examination, it would certainly be discovered by any one searching for amoebae.

The two cases here presented were probably infected in Europe. They are brothers, five years and three and one-half years old. The children of American parents, they have spent most of their lives in Paris, being taken on motor trips through Northern Italy, Switzerland and Southern Germany in the summers. Two years ago, the younger boy began to have a distended abdomen. One year ago, the elder boy also began to have intestinal indigestion. Last summer they came back to this country and were seen by us just as they were getting over mild attacks of whooping cough. Both boys were in fairly good condition, but were losing weight. Their appetites were capricious, their bowels irregular, their stools foul smelling and their urines loaded with indican. There was no mucus in their stools and Schmidt's fermentation test was negative. Both boys showed 80 per cent. Haemoglobin. In November encysted *Lamblia* were found in their feces and the children were put on a moderately restricted diet in order to clear up the intestinal indigestion. In December they were started on small doses of calomel, followed by magnesium citrate twice a week. Now, in February, 1912, their appetites are improved and the younger boy is gaining weight. The older boy still has some intestinal indigestion.

The stools of the younger boy have from the first shown *Lamblia* cysts. Before the calomel they were present in enormous numbers, averaging perhaps two cysts to a No. 7 Leitz field. Since the calomel, the cysts have been fewer, and in the last specimen were hard to find.

The older boy on the first two examinations showed no cysts. Later they appeared in large numbers. Shortly after calomel was started, they disappeared for a time, but the last examination showed them present again.

In both cases kite-shaped forms were found only when a laxative was given and the stool examined on a warm slide as soon as it was passed. Only a few actively motile forms were found after a prolonged search.

Summary: The *Lambllia Intestinalis* is a parasite of doubtful pathogenicity which is fairly common in Europe, but seldom found in America. Possibly it is overlooked on account of the fact that it usually appears in the cyst form, which is very small and not unlike some vegetable cells. The two cases here reported, the fourth and fifth in this country, were probably infected in Europe.

Discussion.

DR. I. ADLER: I would like to ask whether there is any eosinophilia in the blood. As a rule, and as yet unexplained, all the intestinal rhizopods, such as amoebae and the like, produce no eosinophilia, while the flagellatae, as far, at least, as is known to me, are usually associated with considerable eosinophilia in the current blood.

DR. MARTLAND: I have a case of infection with *Lambllia* at the present time, which was referred to me by Dr. John B. Murphy, of Chicago, for the purpose of making repeated examinations of the feces for *trichomonas intestinalis* and tubercle bacilli. The patient is a single woman, about 25 years of age, who has had an obstinate diarrhoea of over six years' duration. She had consulted several physicians in New York, Chicago and abroad, and spent a large part of this time in private hospitals and sanatoria. She had had repeated examinations of the urine, feces and gastric analysis made.

I first examined her specimen of feces for five successive days and at all times the stools were loose; there was no formation of scybalae at all. At all times there was found an enormous num-

ber of the flagellated forms, together with a very large number of the encysted forms.

The patient was ordered to bed for ten days and kept on sterile food, consisting mostly of milk. She took an enema, morning and night, in the knee chest position, consisting of 3 pints of hot water containing 8 grs. of methylene blue.

A capsule was given, one hour after each meal, three times a day, consisting of:

Methylene blue gr. 3
Quinine tannate gr. 2
Bismuth subgallate gr. 10

In addition, calomel, gr. 1/30, was given, one hour after meals, three times a day, on the first day, skipped for three days and repeated in a like manner.

At the end of ten days the feces were examined for four successive days, and no *Lamblia* were found, the patient being on regular diet, and the medication stopped.

A second similar course of treatment was pursued for another ten days, and negative examinations resulted.

The patient is now remaining in bed, and taking saline enemas twice a day, and large doses of bismuth subcarbonate.

She has been constipated most of the time, with several well formed stools and no *Lamblia* can be found.

She had no eosinophilia.

DR. W. G. MACCALLUM: It seems to me, for our instruction, it would perhaps be easier to find out what it was that cured the patient, if you gave one thing at a time.

What, Dr. Du Bois, have you learned further, if anything, as to the study of the tissues? Has there been a single case investigated as far as the intestinal wall? Is there any further history of this *Lamblia* other than the two stages—the encysted and the actively motile form?

DR. DU BOIS: Only one man, Zabel, *Arch. f. Verdauungs-krankheiten*, vii. 1901, p. 509, I believe, has published description

of sections after autopsy. He shows elaborate pictures of the *Lambli*a attached to the mucosa by the flagellae. There is no evidence of stages other than the cyst form and the motile form. Grassi swallowed some of the cysts and later developed an infection with the organism.

We regret to say that eosinophiles were not counted in these two cases. In other reported cases the eosinophile count has not been increased.

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4

PNEUMONIA AND ABSCESS OF THE LUNG IN A CHILD.

W. P. NORTHRUP, M.D.

I think this case is of some value as showing how the demands of the clinician were at once answered by the autopsy maker. The presentation consists mostly of the X-ray pictures which demand that certain things shall be found and that they were subsequently found.

This case is a child 17 months old; was sick 21 days in the hospital, was sick 3 days before, making 24 days of sickness. First stage ordinary cold—coughing, sneezing, and hoarseness.

Then it enters upon a second stage quite different from the first; the child showed symptoms of a sepsis. Child became very sick—pulse was rapid, respiration increased; the temperature reached in these next 11 days 106° , fluctuating from 101° to 106° . At the end of this second period of fluctuating septic temperature with prostration, the child entered upon a third stage, namely, a stage which was more or less uniform, steady temperature—high, 104° , with disturbed respiration—pulse ratio, and went four or five days upon this distinctly pneumonic course, with symptoms of developing broncho-pneumonia. It later went on to a fourth stage in which the child seemed to pass a crisis, to improve and promise to get well; and then it died.

The first stage I have no X-ray picture of, the ordinary cold; the second stage I have a distinct picture of—the heart side has distinctly a shadow of consolidation. The child came to the hospital at the beginning of the second period. We believe this circumscribed shadow to be an abscess. It does not touch the heart; it lies just in the plane which you see. Then, in order to find out how deep it was we went to work and took one lateral picture. The abscess shadow lies in the very center of the lungs.

It was perfectly obvious that the child was prostrated by a very severe illness. We fancied there was an associated influenza. We made the diagnosis of abscess due to influenza bacillus. We proceeded to put in a needle and could find absolutely nothing. After a little we took another picture; here, you see, is the third stage; that is distinctly a pneumonia, a very extensive shadow. Now there is a fourth stage in which there was very much more pneumonia, which we could not picture because the child was too ill to allow it. There was evidently an abscess, but we could not find it. We searched the mouth and sputum and everything we could get up from coughing we sent to the laboratory, but could find nothing. But to me it seemed perfectly obvious that there was an infection of influenza. We believed the abscess was probably due to an influenza. Then it went on, as I said, to a case of pneumonia, and after it had seemed to be on recovery from pneumonia, almost like a crisis, it suddenly died.

Immediately after death, fearing that we might not get an autopsy, I got a very large needle and probed in every direction, with those X-rays before me. In the autopsy, to my great satisfaction, they did find two abscesses about the size of beans, that is, they were technically abscesses, but they were not large enough to satisfy me. This first shadow was fully accounted for by what we found at autopsy, namely, these little cavities, and all about little necrotic areas with a little tissue between not yet broken down. There was a formation of partially organized fibrin within the alveoli.

So, looking backwards, we feel satisfied that our first diagnosis verified that the primary lesion was influenza, with an influenzal abscess, and the pneumonia a secondary development. I believe the only lesions of the body were in the lungs.

Discussion.

DR. MACCALLUM had performed the autopsy for Dr. Northrup and found that there was extensive consolidation of nearly all of the upper lobe of the lung, which was curiously mottled with opaque yellow patches. There were numerous holes in the pleura produced by the needle. On section the opaque areas had extended into the lung and in places showed liquifaction of their central portions.

Dr. Soper was able to discover two types of bacteria—pneumococcus and influenza bacillus. The latter grew in the first culture but could not be grown again. Histologically, the lung shows lobular pneumonia in certain areas, of which there is necrosis of the tissue and liquefaction. It resembles the condition seen occasionally in acute glanders of the lungs. About these areas there are alveoli in which the fibrin has assumed a very solid form and has become organized by an invasion of connective tissue cells.

CHOLESTEATOMA OF HORSE'S BRAIN.

ELI MOSHCOWITZ, M.D.

The horse had given symptoms of blind staggers for some weeks previous to death. After a delirious attack in which he smashed four stalls, he was shot.

At autopsy, both lateral ventricles were completely filled with masses which fitted accurately into the cavity. These could be removed and replaced, like a ball in a socket. On the left side the mass was attached by a thin thread to the pia; on the right side the mass lay entirely free. Both masses were practically identical in shape and structure. They were the size of a hen's egg, ovoid in shape, and perfectly smooth. They were white in color, both externally and on section. The consistence was soft, and on section the cut surface was smooth, slightly granular, and uniform.

Microscopic examination revealed a thin fibrous capsule and a stroma which consisted by loosely distributed small, round cells, cells of the plasma type, and a considerable number of polymorphonuclear leukocytes. The tumor was rich in small, well-formed blood-vessels. Throughout the section are numerous spaces discreetly distributed. These spaces are large and are made up of smaller wedge-shaped spaces, which are in a parallel or fan-like arrangement. The spaces are empty in the stained specimen, but are filled with closely wedged cholesterol crystals in the frozen section.

According to Kitt (*Pathologie der Tierén*), these tumors are known among veterinarians as "cholesteatoma vasculosa," although they do not resemble in the slightest way the cholesteatoma met with in the human being. The true nature of these growths is not known. Certainly, the microscopic picture and the physical characteristics strongly suggest an inflammatory origin, and this is further corroborated by the fact that these growths frequently occur in cases of chronic glanders and streptococcus inflammations of the nose.

CASE OF CONGENITAL OBLITERATION OF THE BILE DUCTS.

ELI MOSCHICOWITZ, M.D.

The patient was a three months old female child and was jaundiced from birth. The jaundice at the time of death was deep, although the skin was not green. The child gained very slowly, although it was breast fed, and did not appear or behave very ill until about 24 hours after admission, when the child began to vomit frequently and soon succumbed. Dr. Alfred F. Hess, during life, demonstrated pancreatic ferments with the aid of his duodenal catheter, and diagnosed congenital obliteration of the bile ducts.

At the autopsy, this diagnosis was entirely confirmed. The gall bladder was almost completely obliterated, only a small lumen, holding about a drop of clear watery fluid, persisting. The hepatic, cystic and common bile ducts were completely obliterated and were transformed into dense fibrous cords. In the duodenum there were two papillae. The upper corresponded to the obliterated common duct and was completely obliterated. The lower, about half an inch from the upper, showed a small opening which led into the Duct of Wirsung. The liver was enlarged, firm, and dark-green in color. The surface was slightly nodular. On cut section a distinct cirrhosis was apparent. There was no gross dilatation of the intrahepatic bile ducts. The portal vein and hepatic artery were normal. The spleen was slightly enlarged. The pancreas, kidneys and intestines were normal.

Microscopic examination showed a marked increase of the periportal connective tissue with an abundant new formation of bile ducts. The intracellular bile ducts were greatly dilated and filled with green masses of bile. The parenchyma was otherwise normal. Sections of the other organs showed nothing noteworthy.

ON THE PRE-CANCEROUS STATE—AN EXPERIMENTAL STUDY.

I. LEVIN, M.D.

By a pre-cancerous state we understand a condition of chronic inflammation or other abnormality of the tissue in which cancer develops. This condition immediately preceding the growth of the tumor, presumably has, at the same time, a causative relationship to the development of the cancer. The following points must be considered in the study of the pre-cancerous state: In the first place, does the condition found on morphological study of the early stages of cancer actually have a causative relationship to the development of cancer? Further, does the change in the tissue always take place in the beginning of a cancer growth? And, third, which changes in the tissue are to be interpreted as a pre-cancerous state?

The region in which cancer develops consists of two parts—the group of proliferating cells and the normal tissue surrounding the cancer.

Now, under the term “the pre-cancerous state” one may understand an abnormal condition of a group of cells which are subsequently transformed into cancer cells, or a change in the normal tissue surrounding the growing cancer. While at present most investigators admit the existence of a pre-cancerous state, the opinion is divided as to which part of the tissue is involved in the process.

The school of Ribbert and his pupils consider practically only the changed condition in the tissue surrounding the growing cancer; they claimed, until very recently, that any normal cell may become cancerous provided the condition of the surrounding tissue is favorable to it. On the other hand, Hansemann, Orth and other writers maintain that only the cell which subsequently becomes cancerous undergoes a pre-cancerous change. They claim that a normal body cell must undergo certain preliminary changes before it becomes cancerous.

In his recent article on the different conditions of the pre-

cancerous state, Orth distinctly states that the condition of the surrounding tissue has nothing to do with the development of cancer. Only that group of epithelial cells which subsequently develop into cancer undergoes a preliminary pre-cancerous change.

The morphological study of human material cannot settle the divergence of the opinions. The tissue surrounding a growing cancer may be changed, but it is impossible to ascertain whether the surrounding tissue first becomes abnormal and then the cancer develops or whether the cancer development influences the surrounding tissue and it consequently becomes abnormal.

There seems to be more promise in the study of the subject when the material to be used is the transplanted cancer in animals. It is true that here we can consider only the conditions of the surrounding tissues. The group of cancer cells is brought from outside preformed. Consequently we cannot study by the aid of experimentation a pre-cancerous state which would consist in a changed condition of normal cells which subsequently transform into cancer. The existence of such a pre-cancerous state is impossible, as Orth states, to ascertain until the time that we can artificially produce cancer from normal cells. One must confine himself, then, only to the condition of the tissue surrounding the growing cancer cells. The condition of the surrounding tissue is apparently of utmost importance in the development of cancer, since animal study has shown that an inoculation of the same tumor tissue completely fails in a certain number of animals. This phenomenon must be due to the fact that the tissue surrounding the inoculated tumor reacts differently in different animals. This reaction is general in its nature and affects the whole organism of the host. Now, if it were possible to find conditions in the same animals where a local inhibiting influence may be exerted upon an inoculated cancer, while the rest of the animal is apparently susceptible to the growth of the cancer, such a condition would show the existence of a pre-cancerous state as a condition of the normal tissue surrounding the cancer.

In view of this idea, and in view, furthermore, of the fact

that my former studies on inoculation of cancer in different organs showed that while Ribbert's ideas on the value of a reaction of the surrounding tissue may be right, this influence does not consist in a new formation of connective tissue surrounding the growing cancer, and it seemed of importance to search for local influences of the normal tissue upon a growing cancer. During the course of studies on inoculation of cancer in different organs, a tumor was found, an adeno-carcinoma of a rat, which, while it readily grows when inoculated into animals subcutaneously, fails to grow when inoculated into a normal testicle. Here, then, was a purely local condition of resistance of a certain tissue to growth and development of cancer. The question occurred whether it were not possible to change the condition in that special organ in such a way as to render it susceptible, artificially, to the growth of cancer. The experiments consisted in the following three series:

First: To prove positively the contention that the cancer would not grow in a normal testicle, forty animals were inoculated and only in one of the animals did the tumor grow. The testicles were all examined microscopically; most of them showed a peculiar condition of complete necrosis of the testicular tissue and complete disappearance of the inoculated tumor.

Next the testicles were treated with certain substances previous to the inoculation. Scharlach R oil was injected into the testicle. The organ upon the injection changed so that there occurred a great deal of new connective tissue formation and besides the epithelial elements were changed to a greater or lesser degree. In some testicles the tubular cells were practically normal, but surrounded by a great deal of connective tissue. In others the tubules were greatly changed, the cells were in a state of coagulative necrosis, and the structure of the tubules was practically gone. Now, of the thirty-two testicles that were thus treated, subsequent inoculation of tumor was successful in nine testicles, *i. e.*, in 28 per cent. of the animals used. The most interesting phenomenon in connection with this series consisted in the fact that tumor growth took place in these testicles where

the change of the cellular elements of the tubules was the greatest, *i. e.*, where the epithelial cells were in a state of necrosis. In the other testicles where there was just as extensive connective tissue formation but where the cells in the tubules were normal, the tumor did not grow.

The third series of experiments consisted in an injection into the testicle of a 4 per cent. emulsion of ether in water. The experiment was repeated on twenty animals in the testicle. This substance apparently produces a greater lesion in the testicle than Scharlach R oil. While the connective tissue growth was just as extensive as in the testicle treated with Scharlach R oil, in these testicles one finds a great deal more frequently complete degeneration and necrosis of the cellular elements of the tubules. Of the twenty testicles treated previously with ether water, the tumor grew in 65 per cent. of the animals used.

Thus the three series of experiments represent a condition where a normal testicle resists the growth of inoculated cancer while the animal itself is apparently susceptible, and, furthermore, it is possible, artificially, to change the condition of the testicle so that the organ tissue is artificially rendered susceptible to the development of cancer.

LANTERN-SLIDE DEMONSTRATION.

It seems then that we succeeded here in inducing artificially in the testicle a pre-cancerous state by, *i. e.*, a state of the tissue surrounding the tumor graft which renders it susceptible to the growth of inoculated cancer. These experiments also show clearly that this condition of local susceptibility, the pre-cancerous state, is not due to the development of newly-formed or changed connective tissue surrounding the tumor growth, but consists primarily in a certain change of the parenchymatous cells of the organ, a change which removes its inhibiting power against the growth of cancer. It would thus seem that Ribbert's ideas may have to be changed, that the connective tissue change is not specific or primary in the pre-cancerous state, and that the "pre-cancerous" impairment of the normal resistance of parenchymatous cells is of great importance in the development of cancer.

Discussion.

DR. MACCALLUM had felt some hesitation in using the term "pre-cancerous stage" and had suggested to Dr. Levin that "pre-cancerous state" was at least preferable. It seems possible to regard this production of fibrous tissue, etc., as the establishment of a locus minoris resistentiae such as may give rise to the development of a localization for bacteria in places where otherwise these bacteria would not tend to produce lesions. The discussion leaves out of consideration entirely for the moment the obvious fact that the cancer cells are cells of very different biological characters than the normal.

THE SIGNIFICANCE OF THE PATHOLOGICAL OCCURRENCE OF ANISOTROPIC LIPOIDS.

FREDERICK HANES, M.D.

No one contends to-day that the fat which is so constantly found in injured cells is directly derived from a degeneration of the cell. Researches of the past few years have proven that the presence of excessive amounts of fat in cells is always due to a process of accumulation or infiltration. The acceptance of this conception has aided greatly in the elucidation of a problem which has been generally misunderstood since the time of Virchow.

It is to another and newer phase of the question of fat infiltration, however, that I wish to direct attention this evening. In 1902 Kaiserling and Orgler (*Virch. Arch.* 167, 296) while studying the fat in the kidney in a case of chronic parenchymatous nephritis, discovered that some of the fat was not neutral fat, for when placed between the crossed Nicol prisms of a polarizing microscope, it was doubly refractile, anisotropic, whereas neutral fats are isotropic. Mettenheimer many years before had made similar observations, and after him Beneke and Apathy.

Kaiserling and Orgler studied the occurrence of these anisotropic fatty substances under physiological and pathological conditions. They found that the fats of the adrenal cortex were in part anisotropic and that they belonged to the class of substances which Overton has called lipoids. In 1910 Aschoff (*Ziegler's Beiträge*, 1910, 47) summarized the previous work of others upon the question of the accumulation of lipoids in the tissues under various pathological conditions, and on the basis of his own and Adami's investigations he was able to say that the anisotropic lipoid substances found in the body are usually esters of cholesterol. Other lipoids may show anisotropism, but cholesterol esters are the only ones which constantly do at body temperature. Aschoff therefore divides fat infiltration into glyceryl ester, and cholesterol ester infiltration. He recognized the possibility of a third type due to infiltrations with other lipoids (lecithin, etc.), but owing to the rudimentary condition of our chemical and pathological knowledge of these substances he did not discuss them in detail.

Kawamura (*Die Cholesterinesterverfettung*, Fischer, 1911), a pupil of Aschoff, has developed the conception of cholesterol ester infiltration in a monograph to which I must refer you for details.

This hasty and imperfect summary of some of the more outstanding contributions will serve to direct your attention to this newly developed phase of fat infiltration, and full literature lists will be found in the articles mentioned, especially in the monograph of Kawamura.

In the limited time at my disposal, I can only refer to two points of interest in regard to the anisotropic lipoids, namely, their optical properties, and the pathological significance of their occurrence. If some of the detritus of an atheromatous patch in the aorta be examined between crossed Nicol prisms, one sees many small spherical bodies divided by a dark maltese cross into four brilliantly illuminated sectors, that is, they are anisotropic. Such globules, according to the careful researches of Lehmann and Schenck, are fluid crystals. They are of a fatty nature and

are regarded by Aschoff and Kawamura as esters of cholesterol, probably cholesteryl oleate.

In the demonstration room I have placed a polarizing microscope fitted with a Reichert warm stage which is supplied by a syphon arrangement with either hot or cold water as desired. If, while examining these brilliant fluid crystals, one allows hot water to flow through the stage, the beautiful anisotropic phenomenon gradually disappears and the entire field becomes dark. The thermometer shows that the globules pass from the fluid crystalline, anisotropic phase into the fluid, isotropic phase at near 40° C. If one now allows cold water to flow through the stage, the former brilliant picture is restored; the globules have assumed the fluid-crystalline form again. This is truly a remarkable phenomenon, but one which fortunately for us is perfectly familiar to physical chemists, who have carefully studied many such fluid crystalline bodies. I must refer you for details to the excellent monograph of Schenck on "*Kristallinische Flüssigkeiten u. flüssige Kristalle*" (Leipzig, Englemann, 1905).

Aschoff and Kawamura think the heat phenomenon just described is characteristic of cholesteryl esters, and it thus affords a quick and easy method for their recognition. The problem is new, however, so generalizations should be accepted with critical caution.

As to the pathological significance of the finding of such anisotropic lipoids in the tissues, all writers are agreed that they only occur in connection with chronic processes associated with cellular necrobiosis. They do not occur in frankly acute processes. They have been found, for example, in atheroma, chronic nephritis, chronic salpingitis, in many pyogenic processes, actinomycosis, many tumors, especially hypernephromata, etc. (vide Aschoff).

The macroscopic and microscopic recognition of these substances would seem to offer a diagnostic aid in many conditions, and every pathologist should familiarize himself with the properties and occurrence of these anisotropic lipoids.

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DR. W. G. MACCALLUM, *President.*

REPORT OF THE COMMITTEE ON MICROSCOPY ON DR. JESSUP'S SPECIMENS OF PLASMA CELL TUMOR OF THE TONGUE.

We are disinclined to regard the process as a neoplasm and offer the diagnosis of *chronic granuloma* of unknown origin, for the following reasons:

The long duration of the process.

The wide local dissemination of the lesion.

The existence of a process in the rectum, probably of identical nature.

The microscopical picture is that of a granuloma, not a true neoplasm. The cells are of typical form without excess of chromatin or marked variation in size. They loosely infiltrate the perivascular tissues, fat tissue, and muscle bundles. The lymphocytic or plasma cell infiltration is chiefly superficial, suggesting the action of an irritant passing in from the surface.

The muscle tissue shows extensive degeneration followed by fibrosis, and foci of fibrosis appear in the wide cellular areas. These changes in the muscle, especially, seem to us incompatible with the diagnosis of sarcoma and to indicate the inflammatory nature of the process. The entire lesion suggests the possibility that there was some obstruction to the circulation in the deeper portions of the tissue not included in the sections.

DEMONSTRATION OF SPECIMEN OF MEGACOLON.

CHARLES NORRIS, M.D.

Dr. Charles Norris presented a case of Congenital Megacolon or Hirschsprung's Disease. The case will be reported in detail by Dr. Wilcox.

The specimen came from a male child 18 months of age, who had been subject to constipation since the age of three weeks; for the past year had been treated at dispensaries for constipation. There were no natural movements during his week's stay in the hospital. The abdomen was greatly distended, the abdominal wall being very thin, due to extreme stretching. On cutting through the abdominal wall, the entire upper portion of the abdomen was occupied by a greatly distended transverse colon and cecum. The

dilatation ceased abruptly at the splenic flexure, the descending colon and sigmoid being of normal appearance and dimensions. The dilatation commenced in the cecum at the ileo-coecal valve, the small intestines being normal. The dilatation is greatest at the middle portion of the transverse colon, the gut being in this situation 21 cm. in diameter. Wall of the dilated gut is thickened, its mucous membrane is everywhere smooth, showing in a few places patchy, mucosal hemorrhage. The gut contained a large amount of extremely frothy material which was light colored and greasy. At the splenic flexure there was a valve-like fold at the junction of the distended and undistended portions of the colon. Dr. Norris considered that there was a partial valve-like closure at the splenic flexure which had led slowly to the distention and hypertrophy of the gut. Sections taken from the distended gut show marked hypertrophy of the muscular coats, mucous membrane being normal except for the hemorrhagic spots referred to above. The other organs showed no lesions of interest. The case is an unusual one for the reason that the sigmoid flexure was not involved.

Dr. Norris presented a series of large intestines, showing different lesions of this portion of the gut, namely, a case of Suppurative Colitis; a case of Ulcerative Amoebic Colitis; a case of Chronic Suppurative Typhlitis, which was discovered in a patient dying of hemorrhage from the rupture of a blood-vessel at the base of a typical round ulcer of the duodenum; and an interesting case of Acute Phlegmonous Typhlitis in a colored man forty years of age, in which *Bacillus Coli Communis* was obtained in pure culture from the spleen; there was, besides the lesion of the gut, a typical atrophic cirrhosis of the liver with an extremely small left lobe, which was considered to be an anomaly.

Discussion.

DR. F. C. WOOD thought that it was interesting to realize how very rarely these cases of terminal colitis in nephritis are recognized clinically. He had never seen one positively diagnosed

before death. If the stools were carefully examined it should be easy to make the diagnosis, because there must be a considerable amount of blood, debris, and mucus.

DR. MACCALLUM thought that the liver which Dr. Norris exhibited showed changes similar to those described by himself some years before. The atrophy of the left lobe might be regarded as the effect of a toxic or infectious injury rather than a congenital anomaly on account of the large size of the afferent portal vein. He suggested that it would be interesting to know whether there were evidences of a regenerative hypertrophy in the right lobe.

Phlegmonous colitis is a condition which has been recorded relatively seldom but seems to resemble in its mode of production the other forms of phlegmonous enteritis which sometimes occur higher up in the intestine. In cases which he had observed almost every one showed streptococci in the submucosa with minute perforations of the mucosa itself.

DR. CHARLES NORRIS: I am very sorry that I have neglected to cut the left lobe of the liver; I will do so as soon as I can. Of course, it is very true that colitis is often an accidental finding and it is especially so in the cases where there is ulceration near or involving the rectum. In this case, the diagnosis was not made at all, although the ulcers at autopsy were near the marginal ring.

A SIMPLE METHOD FOR OBTAINING THE ALPHA-NAPHTHOL OXIDASE REACTION IN LEUCOCYTES.

FRANCIS CARTER WOOD, M.D.

Recent studies of so-called acute lymphatic leukemia by Longcope, Schultze, and others have shown that some of the large cells previously considered to be leucocytes carry an oxidase ferment easily demonstrable by certain reagents. The substances usually employed are a 1 per cent. aqueous para dimethylphenyl-

endiamin (also known as para-amidodimethylanilin) and a saturated aqueous solution of alpha-naphthol. Equal volumes of these solutions are mixed and poured over a slide which has previously been fixed with formalin, not with alcohol. Old smears do not require any fixation. Bone marrow cells carrying the oxidase ferment take a brilliant blue stain under these conditions, the dye affecting the granules chiefly. The lymphocytes do not show any color.

In a study of a number of cases I have found it difficult to keep the free base which is ordinarily recommended, and this trouble has also led to the suggestion in Germany that the amount of the para-amidodimethylanilin required for each test should be obtained sealed in glass tubes. It is possible, however, to avoid this difficulty by a very simple procedure. While the base and the hydrochloride of para-amidodimethylanilin are difficult substances to keep and handle, the sulphate, which is easily made up synthetically by the reduction of the indicator methyl orange either with stannous chloride¹ or, as suggested by Fischer², with ammonium sulphide, is a crystalline dry powder which is very easily measured out or weighed in small amounts, and has kept perfectly in a stoppered bottle for several years in my experience. A small quantity of this powder is dissolved in about 1 to 2 c.c. of normal sodium hydrate. The alkali decomposes the salt, setting free the base. An equal volume of 1% aqueous alpha-naphthol is added, and the mixture is ready for use. The presence of such a considerable quantity of alkali does not interfere with the reaction but rather hastens it. Within a few seconds after the reagent has been poured on the slide, the bone marrow cells will take a deep blue color. If the reaction is too rapid, 1.5 c.c. of normal acid can be added to neutralize the alkali partially, but I have found the solution in normal sodium hydrate to be perfectly satisfactory.

¹GATTERMANN: *Die Praxis des organischen Chemikers*.

²FISCHER: *Ber. d. deutsch chem. Gesellsch.*, 1883, xvi, 2234.

UNUSUAL TUMOR OF THE LYMPH NODES.

FRANCIS CARTER WOOD, M.D.

This specimen is one of considerable interest from both the diagnostic and the prognostic aspects. It consists of several moderate sized lymph nodes removed from the axilla of a patient otherwise perfectly healthy. Clinically the case is one of typical Hodgkins' disease, showing some anemia but no other disturbances. The nodes were encapsulated and freely movable. On section they were rather opaque and showed no necrosis.

Microscopically the nodes are composed largely of cells of an epithelial or endothelial type lying in strands and masses throughout the tissue. There is no connective tissue about the individual cells. Some of the normal lymph structures are still retained; the germinal centers show well in some of the sections; and there are areas of perfectly normal lymph tissue. Some of the peripheral sinuses are completely filled with cells of the tumor and these cells are also to be found in some of the blood vessels in the capsule. There are also strands of the cells in the somewhat thickened capsule itself. There is very little connective tissue reaction in the nodes, not nearly as much as is generally seen in Hodgkin's disease. Occasionally mitoses are found in the large cells. Some of these cells are multinucleated, resembling very much the large cells of Hodgkin's disease. There are no eosinophile cells in the tissues. No bacteria could be demonstrated after softening some of the tissue with antiformin.

It is not easy to make a definite diagnosis on this material, and I feel that much must be decided by the clinical course of the case. One pathologist who has seen the specimen is quite certain that it is a case of Hodgkin's disease in a rather early stage; others, including Dr. William H. Welch, have considered the specimen to be of a sarcomatous nature. I have never seen a tumor exactly like this in morphology, though some ten or twelve years ago a somewhat similar specimen came into my possession, but in that the vascular development was considerably greater and the cells were arranged in close contact with capillaries, suggesting hemangiosarcoma. The invasion of the node also was less diffuse and more nodular than in this case.

Very little of similar cases can be learned from the literature on Hodgkin's disease or sarcoma of the nodes. A few cases, probably similar to this, have been described, but inasmuch as the reports are illustrated by drawings and not by photographs it is difficult to say just how close the resemblance is. Personally, I am rather inclined to consider this a cellular hyperplasia of a tumor nature, but it is not impossible that the case will finally develop into a typical Hodgkin's, with lesions in other nodes.



FIG. 1—Section from the periphery of lymph node, showing large cells filling sinuses. (x 250.)

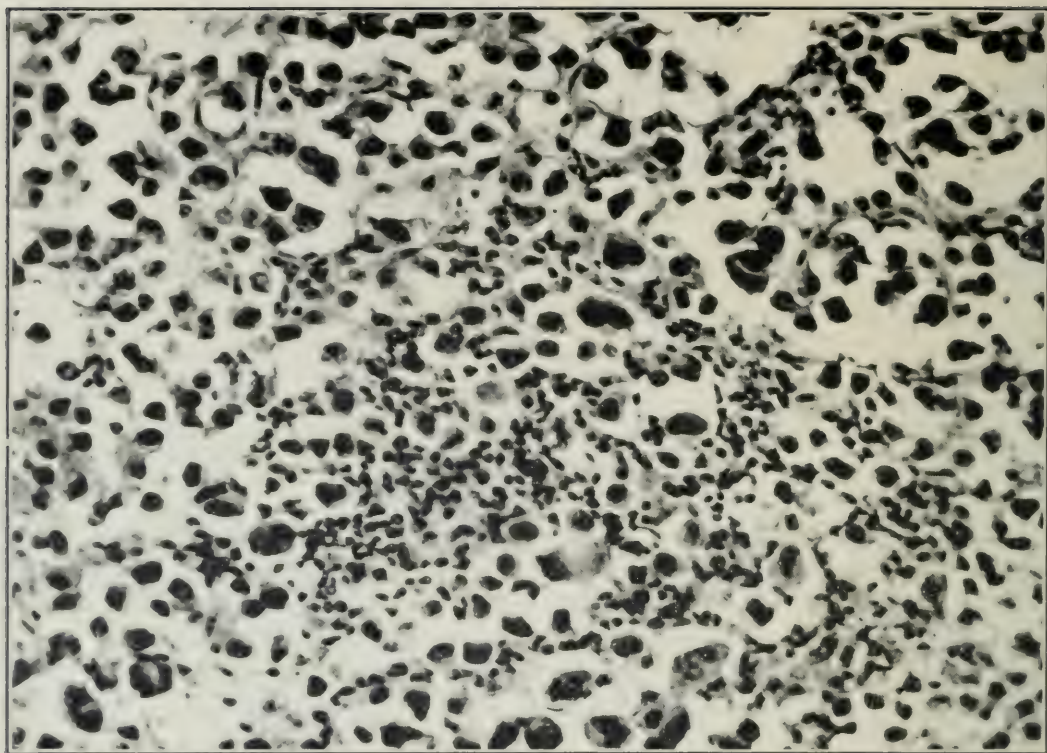


FIG. 2.—Alveolar portion of growth replacing the lymph structure. (x 250.)

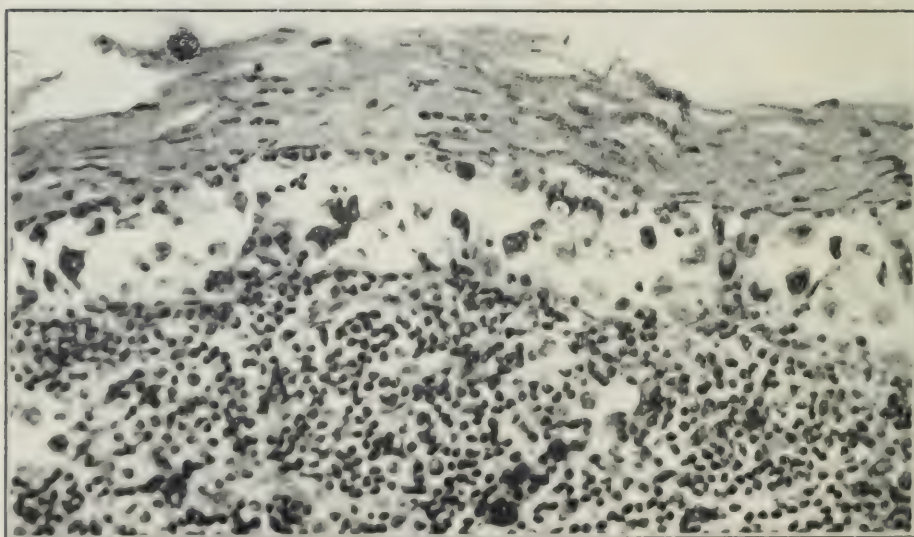


FIG. 3.—Invasion of peripheral sinus of lymph node of cells. (x 250.)

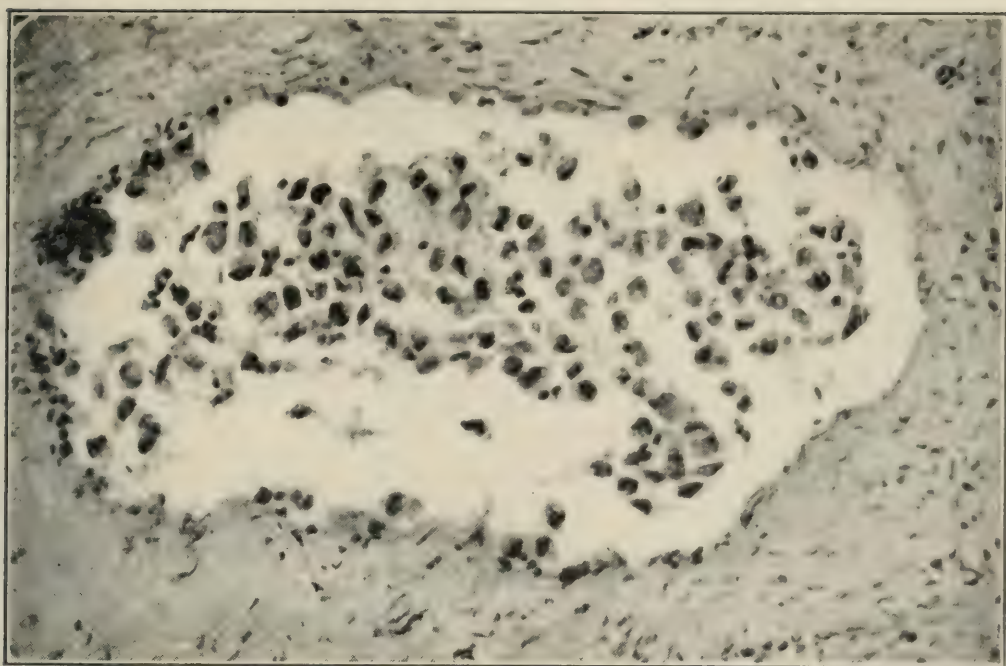


FIG. 4.—Blood vessel in perinodular fat with lumen filled with large cells of the same type as the tumor. (x 250.)

A CASE OF SO-CALLED "KRUKENBERG'S" TUMOR OF THE OVARY.

MORTON E. HALL, M.D.

I wish to present a very interesting case of malignant tumor of the ovary which resembles in its histology the so-called Krukenberg tumors of the ovary. To Dr. Arthur Reich I am much indebted for obtaining an accurate and concise clinical history of the case as follows:

The case was brought to Bellevue Hospital in a serious condition on February 1st, 1912. Clinical history: Nellie D., age 32, married, native of England, a trained nurse; for past two or three years had been working as a cook; previous history not obtainable. Is pregnant approximately twenty weeks; according to husband she had become dull and made incoherent statements,

had severe morning vomiting for the past five months of the pregnancy. No loss of weight was noted.

For past two weeks patient had been vomiting and had great epigastric distress. For forty-eight hours prior to admission, she was in a semi-comatose condition, had severe headaches.

On admission patient was irrational, presenting the picture of a psychosis. Skin and mucous membranes were markedly dry, conjunctivae intensely inflamed; considerable emaciation; no oedema. Had general abdominal pain without any particular points of tenderness or rigidity. Height of fundus was 5 cm. below umbilicus. No foetal heart sounds heard but foetus could be palpated. Cervix was large and soft; external os not dilated. Posterior fornix was thickened and firm.

Temperature on admission was 97.3 and ranged between 97-99.2. Pulse 72-100, of poor force, low tension and small volume (B. P. .80). Respirations rapid and shallow.

On admission 5 oz. of heavy, dark brownish urine were obtained by catheter, containing albumin and many casts—sp. gr. 1030. During last 58 hours, patient excreted 2 oz. of urine. Patient was catheterized several times with no result. Patient continued in a semi-comatose condition, with delirium, which soon passed into a deep coma, from which she could not be aroused.

Findings after admission: Patient had a convulsion which was general and tonic in character, lasting two minutes. Manual and instrumental dilatation of cervix was performed, and a macerated foetus was extracted of about twenty weeks' gestation. Patient died ten hours after induction of labor. A diagnosis of toxæmia of pregnancy was made.

Autopsy performed by Dr. Charles Norris February 6, 1912, forty-eight hours after death. Body 158 cm. in height, fairly well developed and nourished; there is considerable pallor of the skin; no oedema of the subcutaneous tissues. Breasts are large and contain milk. Peritoneal cavity contains no fluid. There is a moderate amount of panniculus abdominus. Pelvic cavity is nearly filled by the enlarged uterus. On the peritoneal surface

of the diaphragm and parietal peritoneum there are extensive flat, firm, whitish, slightly elevated plaques, which are most numerous and largest on the diaphragm and small, circular, 1 to 2 mm. in diameter foci. Lungs everywhere slightly emphysematous and hyperaemic. In the left upper lobe there are a few small areas of lobular pneumonia. There is no evidence of tuberculosis in lungs or lymph nodes. Heart is normal except for slight opacities of the endocardium and a few sub-endocardial petechiae in the left ventricle. Liver shows thickening of capsule and slight chronic congestion. Gall bladder, spleen and pancreas normal. Kidneys are somewhat enlarged and soft; capsule strips readily leaving a smooth surface; cortex is wider than normal, pale and opaque, markings distinct. Pyramids somewhat congested. Uterus is large, 15 cm. in length by 11½ cm. in breadth by 4 cm. in depth; thickness through wall 15 mm. Cavity is packed with iodiform gauze. Placental site is free from clot. Left ovary small and sclerotic, measures 3.3 cm. in length, 1.5 cm. in width and 4 mm. thick at its widest portion, with a few small cysts. Left and right tubes show slightly elevated, pale plaques similar to those seen on parietal peritoneum. Similar plaques are found on the serosa of the broad ligaments and on the posterior wall of the cervix. On section the cervix is infiltrated but the mucosa appears normal. The right ovary is large, 6 cm. in length, 4 cm. in width. It is firm, somewhat hyperaemic; section smooth; there are a few small, subcortical cysts. The isthmus of the uterus is large. There is a large right lateral tear of the cervix and numerous cysts are found on the vaginal surface of the cervix. The vagina and labia are normal. Gastro-intestinal tract; Oesophagus normal; the pyloric portion of the stomach, for several inches, is thickened with a firm, tumor-like tissue and there is considerable hypertrophy of the muscular coat of the pylorus. The regional lymphnodes, the peripancreatic and portals, are infiltrated and there are a number of nodes, which are firm, in the mesentery of the large gut. The small intestine contains a good deal of slate colored mucus without blood. There is considerable hypertrophy of the solitary follicles of the lower portion of the ileum. Lowest Peyer's patch is atrophic

but large; mucous membrane of the coecum and transverse colon is extremely congested without ulceration. Rectum normal. Organs of the neck and mouth were not examined. Head: Dura is considerably adherent; there is moderate pial oedema; vessels at the base are normal; no gross lesions of the brain on section. Middle ears and sphenoids normal. The following anatomical diagnosis was made:

Carcinoma of the pylorus of the stomach.

Peritoneal metastases.

Lobular pneumonia.

Acute parenchymatous nephritis.

Acute colitis.

Tumor of the right ovary (endothelioma?)

Postpartum sub-involution of the uterus.

Moderate pial oedema.

Sections of right ovary taken from various parts show a similar microscopic appearance. The outer layer of the ovary is normal ovarian cortex, with a surface layer of low cuboidal cells with deeply staining nuclei (the remains of the germinal epithelium) which in places is absent. The tumor is moderately vascular, consists of a connective tissue stroma composed of fibrils and numerous young spindle shaped connective tissue cells. Lying irregularly among these are large, swollen cells with sickle-shaped nuclei, which are situated at one side of the cell and surrounded by a very small amount of eosinophilic protoplasm. The larger portion of the cell is filled with a homogeneous material, composed of granules (staining with weak aqueous thionin) reddish brown in color. These large cells closely resemble those described by Krukenberg as the signet ring cells. There are also many cells, about a quarter the size of these larger ones, with round nuclei surrounded by eosin staining protoplasm with no evidence of mucin. There are cells which are intermediate in size and shape to those described; they show larger and smaller drops of mucin, surrounded by a ring of eosinophilic protoplasm. Thus we conclude that the signet ring cells are derived from the smaller variety of cells—a conclusion similar to that reached by Krukenberg.

A Van Gieson stain shows the large signet ring cells to be individually surrounded by fine, connective tissue fibrils. This feature led us to believe that we were dealing with a fibro-sarcoma, in which certain of the cells had undergone mucoid degeneration. No normal ovarian tissue was found anywhere in the right ovary.

In the left ovary there was found a small tumor area having a similar microscopic appearance to that described above in the right ovary. There is a sharp line of demarcation between the area of tumor and that of a small corpus luteum cyst.

Sections of the cervix show larger and smaller tumor nodules; the smaller ones are seen to lie in lymph spaces. In no place can any connection be made out between the tumor nodules and the epithelium of the cervix. The smaller nodules show cords of tumor cells distinctly carcinomatous in type. In the larger nodules, however, the central portion shows a structure similar to that described in the ovary, but in the periphery of the nodules one sees cords of rapidly proliferating cells with deeply staining nuclei, which appear to be distinctly carcinomatous. The pelvic lymph-nodes show no evidence of infiltration. Sections of the tube examined, show in the lymph spaces of the serosa a few very small collections of tumor cells, which are carcinomatous in type with no mucoid degeneration.

The peritoneal metastases present a similar microscopic picture. Here the lymph vessels are dilated but none were found with tumor cells. Sections of the pyloric region of the stomach show marked glandular hyperplasia, with acute and chronic inflammatory changes in the mucosa and less marked in the submucosa. There was no evidence of ulceration or infiltration of the mucosa with tumor cells. Muscular layer and submucosa are thickened and infiltrated with tumor cells. Collections of tumor cells vary considerably in size in the serosa of the stomach and in the muscular coat, some being quite large and others small apparently lying in lymph spaces. Collections of tumor cells in the submucosa are very small and in many cases are seen to lie in the lymph vessels. The central portions of the larger nodules

with Van Gieson's stain present the same appearance as described in the right tumor. There are many single cells separated by fine fibrils of connective tissue. As one goes towards the periphery of these nodules, the tumor cells appear more in the form of cords with no inter-cellular connective tissue fibrils; their nuclei stain very deeply with hematoxylin and they appear to be proliferating rapidly. The tumor cells in the submucosa in places have broken through the muscularis mucosae but are not directly connected with the acini; in no place is there any evidence of acinal formation in the submucosa. In the central portion of the larger nodules one sees many typical signet ring cells with marked mucoid degeneration and the transitional stages from the smaller cells to the large signet cells. Towards the periphery in the more rapidly growing portions of the nodules no evidence of mucoid degeneration was made out. Sections of the uterus show the uterine wall to be in the stage of subinvolution.

The case is of interest from three points of view: Firstly, Is the tumor in the ovary primary, or is it secondary to a primary tumor of the stomach; secondly, are the tumor cells epithelial or mesenchymal in origin; thirdly, are we justified in applying the word Krukenberg to this tumor, thereby implying that the growth is primary in the ovary, or should this term be used merely to describe the microscopic appearance of the growth in the ovary and similar growths of this organ as described in the literature?

Krukenberg,¹ in 1896, described six cases of malignant tumor of the ovary, characterized by the presence of signet ring cells, which he claimed were different from any other tumor described up to that time. In the two cases in which an autopsy was performed, peritoneal metastases were found, but he makes no particular mention as to the condition of the stomach mucosa. None of his cases showed any evidence of acinal formation and in no case could he find any epithelial origin for the characteristic signet ring cells. He therefore suggested that the cells were derived from the connective tissue stroma of the ovary. Metastases occurred later, by way of the lymph vessels, into the peritoneum

and stomach. He described his tumor as a fibro-sarcoma, adding the word Mucocellulare to describe the mucoid degeneration of the cells, and Carcinomatoides to explain the high malignancy and epithelial appearance of the signet ring cells.

Our case resembles Krukenberg's first case in practically all particulars except that mucous membrane of the stomach in our case shows considerable glandular hyperplasia in the region of the tumor. There is no evidence of ulceration and no direct relation of the tumor to the mucosa is traceable.

A review of the literature on this subject is decidedly interesting but it is extremely unsatisfactory and not helpful in deciding positively the primary origin of the so-called Krukenberg tumor of the ovary.

In 1902 Schenk² presented a case, with autopsy, which showed a tumor of the ovary with similar gross and microscopic appearance, with metastases in the abdominal lymphnodes, but without a stomach tumor. He found no other focus of origin for his tumor and he thought that it was a primary tumor of the ovary. He expressed the opinion that such primary tumors are rare in the ovary; indeed he accepts only Krukenberg's first case and his own as true primary tumors of the ovary. He gives no explanation as to the origin of the peculiar cells. Sternberg³ and Orthmann⁴ have described cases which they considered should be classified as Krukenberg tumors. Fischer⁵ also described two such cases. These authors agree with Krukenberg as to the primary origin of these tumors, but in no case have they given any explanation or decided definitely as to the origin of the tumor cells.

The conception of the primary origin of these tumors in the ovary is widely disputed. Glockner,⁶ in 1904, collected eighteen cases of ovarian tumor, three of which showed a structure similar to that of Krukenberg's, but also found in each case a pyloric carcinoma which he considered to be primary. Wagner⁷ reported a case of carcinomatous ulcer of the stomach with tumors of the ovaries which he considered secondary. Schlagenhauser⁸ reported four tumors showing primary foci in the stomach, com-

bined with ovarian tumors showing the Krukenberg histological type. He emphasized the fact that, although there may be true primary Krukenberg tumors of the ovary, that metastases of gastric origin may take on this peculiar structure in the ovary. Kaufman,⁹ in his text book, believes that the majority of these tumors are metastatic. Burdinsky,¹⁰ in 1908, described a case of Krukenberg tumor of the ovary associated with a carcinomatous ulcer of the stomach, and considers this case a further argument in favor of the secondary origin of such tumors. Hussy¹¹ described a case of carcinoma of the stomach in which there were definitely formed acini in the ovarian tumor. This case, therefore, seems to us to have no bearing, on the nature of the tumors under discussion. Cohn¹², in studying four cases, has concluded that they are all secondary in the ovary.

The most recent report (and the only one found in the American literature) is one by Outerbridge¹³ of Philadelphia; he reports a case of tumor of the ovary. The description and photographs of the sections of the ovary closely resemble Krukenberg's, and he classes the case as that of a Krukenberg tumor; he states that they are rare but that they may occur primarily in the ovary; he also makes the statement that any tumor of the ovary may undergo myxomatous change, not only in the ground substance, but in the cells.

A review of the literature is of little help in deciding whether or not such tumors do ever occur as primary in the ovary. In many of the cases reported, no autopsy was performed. In our case it would have been difficult to exclude the primary ovarian origin of the tumor with a mere examination of the ovaries. The case of Schenk and Krukenberg's first case are of most particular value and one is led to conclude that these two cases may have been primary in the ovary. But we all know how difficult it is to decide whether there is not a primary tumor in some part of the intestinal tract without thorough microscopic examination. In Krukenberg's first case he leaves us in doubt as to the condition of the stomach mucosa. Outerbridge explains that at operation the stomach was palpated and found normal; we do not believe

that it is possible to decide that there is no tumor change in the stomach mucosa simply by palpation.

Dr. Symmers of Bellevue Medical College has very kindly lent me a section of an ovarian tumor removed at operation; the history of his case is similar to ours, but not complicated with pregnancy. The sections studied showed the signet ring cells, as in our case, but there is considerably more fibrous tissue stroma present. (Further observation of the case was impossible, patient leaving the hospital after operation).

There has been considerable discussion as to the paths of dissemination followed by the tumors, by Pfannenstiel¹⁴ and others. In Krukenberg's first case the lymphnodes were infiltrated, according to him, by way of the lymphatics. Kraus¹⁵ examined a series of ovarian carcinoma and found that the growth always appeared earliest at the periphery of the organ; he concludes that there was a direct invasion through the germinal epithelium by wandering tumor cells. Two of his cases resembled Krukenberg's tumors in histology. Stickel¹⁶ doubts this method of direct invasion and considers metastases to occur by way of the lymphatics. Various other authors have advocated the latter theory. (In our case, although the lumbar and peripancreatic nodes were slightly enlarged, there was no further evidence of tumor infiltration, and one of the pelvic nodes showed on section no evidence of tumor growth). Stauder¹⁷, in the study of twenty ovarian tumors, found three tumors similar to Krukenberg's; one of these cases he considers to be a mixed tumor with areas resembling carcinoma, with other areas resembling sarcoma and myxoma. The second was associated with carcinoma of the stomach, and he considers the ovarian tumor to be secondary. He does not state whether the pyloric tumor showed mucoid change in the cells or not. In his third case he described undoubtedly a sarcoma, and thinks that the signet cells are derived from the connecting tissue stroma of the ovary, and agrees with the suggestion of Krukenberg in this respect. In his case, however, he had no autopsy and so, I think, one can place very little value on this case. Anann¹⁸ reported eighteen secondary ovarian

carcinomas, four of which were like Krukenberg's. Here and there the tumor cells are single, lying in a connective tissue stroma; in other places they appear in cords. This is indeed very similar to our case. He suggests that the ovarian connective tissue undergoes a definite proliferation, due to the irritation of the tumor cells. He does not say whether such a proliferation occurred in the primary focus. In our case I find that it does occur in the stomach tumor.

Rosthorn¹⁹ states that most of these tumors are secondary, but he is convinced that some are primary. He reports a case of fibro-sarcoma with nodules in the skin, lymphnodes, abdomen the thorax, with his lateral ovarian tumor. The latter on section showed a structure similar to Krukenberg's tumor. He considers the primary focus is in the ovary and classes the tumor as a true sarcoma of the ovary, with mucoid changes in the cells. Sternberg²⁰ reported a case (as an endothelioma of the bone marrow) in which the bone marrow was shot with tumor nodules. The ovaries were sclerotic and without tumor infiltration. The cells showed a distinct signet ring formation, as do the Krukenberg tumors.

Rosthorn's and Sternberg's cases prove that tumor cells of a mesenchymal origin may undergo intra-cellular mucoid degeneration as well as those of epithelial origin. These statements do not, however, help us to decide the epithelial origin of these tumors.

Conclusion: In carefully comparing the various stages of the tumor nodules in the stomach and cervix of our case, it is seen that the central portion of the nodule shows the same structure as does all the portions of the right ovary. The periphery of the nodules, however, is slightly different; in the central portion we have various transitions, from the small cells with eosinophilic protoplasm up to the large signet ring cells showing marked mucoid degeneration; in the periphery of the nodules none of the cells show mucoid degeneration; they occur in cords rather than singly, as in the central portion of the nodule; their nuclei stain very deeply with hematoxylin and they appear to be actively proliferating.

From this it would appear that the larger the tumor nodule the more mucoid degeneration there is, and the central or older portion shows alone this change. In the enlarged and completely involved right ovary the structure is the same throughout. The increased intercellular connective tissue present around the signet ring cells, I would suggest, may be a sort of pseudo-sarcomatous change of the ovarian stroma, which is seen only in the older parts of the nodules and elsewhere, namely, cervix, etc. This intercellular fibril formation we maintain is coincident with and has definite relation to the onset of mucoid change in the tumor or parenchymal cell. Although no direct relation of the tumor cells to the stomach mucosa can be made out, I consider, for the reasons advanced above, that we have a primary medullary carcinoma of the stomach with the older parts of tumor showing pseudo-sarcomatous changes and mucoid degeneration of the cells, and that the ovarian tumor is secondary to the gastric carcinoma. The term Krukenberg should alone be applied to the microscopic appearance of a tumor and should not be used to designate a distinct type of primary ovarian tumor.

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Discussion.

DR. F. C. WOOD said that he had seen four or five of these Krukenberg tumors of the ovary, all with characteristic morphology, and in all, the primary tumor was in the stomach or gall-bladder. His personal belief was that ovarian tumors of this type were always secondary, arising from a malignant growth in the stomach, gall-bladder, or intestine. In this connection it was remarkable how frequently there was ovarian involvement in carcinoma of other organs. It was not at all an uncommon occurrence in a case of carcinoma of the breast to find the ovary perfectly normal on gross inspection, and yet on making serial sections to discover nodules of undoubted carcinoma in the lymph spaces.

DR. MACCALLUM thought that it was rather absurd to name these tumors after Krukenberg, since his diagnosis in his own case was obviously wrong. He had seen several such tumors primary in the stomach with widespread metastases which were composed of loosely arranged cells, each one containing a droplet of a colloid substance.

A CASE OF OSTEITIS DEFORMANS.

V. H. NORRIE, M.D., AND GUY WALLACE, M.D.

The case of Paget's disease is one from Dr. Van Horne Norrie's service at Bellevue Hospital. The patient was admitted November 4th, 1911, dying seventeen days later, and presented the essential manifestations of this disease.

The clinical history is very meagre. The man had been a heavy drinker and smoker; gave a history of chancre, without secondaries; had gonorrhea four times; was a veteran of the Civil War, and during the past twenty years had occupied a position as salesman; during the last two years he had been living on his pension. The patient came to the hospital because he was becoming weaker and was unable to take care of himself. A diagnosis of Paget's Disease was made from the massive head. There was but a slight bowing of the right femur, the hands and feet being normal. There was an indistinct history of muscular rheumatism during the previous year. The patient stated that when fifty years of age he wore a No. 7 hat, and that practically every four years since that time he required a larger one. His picture in uniform, taken at the time of the war, shows no enlargement of the face or head. This cranial enlargement, apart from the sensation of weight, caused him no discomfort.

The chief complaints on admission were, a dull aching pain in the back, weakness, and headache. During his stay in the hospital he developed flaccid paralysis of the left arm, with flattening of the left side of the face, and deviation of the tongue to

the left. The radials and temporal arteries were extremely prominent, being practically converted into tortuous pipe-stems. The Wassermann reaction was negative. Broncho pneumonia supervened and, after having been in coma with stertorous respiration for two days, he died.

The autopsy was performed by Dr. Charles Norris the following day and the anatomical diagnosis was as follows:

Cerebral hemorrhage.

Paget's disease.

Chronic and acute pachymeningitis hemorrhagica fibrinosa.

Marked pial oedema.

Extreme arterio-sclerosis of cerebral and coronary arteries.

Chronic emphysema and bronchitis.

Lobular pneumonia.

Acute localized fibrino-purulent pleuritis, left.

Acute fibrinous pleurisy, right.

Slight chronic interstitial and acute parenchymatous nephritis.

Enlarged prostate.

Hypertrophy of the lingual follicles.

Body is that of an old man 70 years of age, 5 feet 6 inches in height. There is considerable emaciation of the extremities and trunk. Thorax is moderately long, conformation normal. There is slight bowing of the legs. The knee joints are of normal conformation. The feet, toes, hands and fingers are normal. Breadth of hand 8 cm. The wrist, elbow, shoulder joints and vertebral column are normal. There is abundant dark hair over the chest; the pubae are abundant, masculine in type; there is considerable perineal hair; small amount of hair over thighs, axillary hair abundant. The hair partly gray, is abundant on the sides and scanty over the top of the head; eyebrows are dark and moderately thick; long grayish beard and moustache. The costal cartilages are of normal breadth. The first costal cartilage is calcified, the other cartilage being slightly greenish yellow on section with only a few calcific foci. The ribs are fragile. Intercostal spaces, ribs and cartilages are of normal breadth. Marrow of

the ribs is abundant and dark red in color. The liver extends about a hand's breadth below the costal arch. Diaphragm is at the fourth space right and left.

Head: Head is very large and heavy, the face being normal in size. The temporal ridges are large and prominent; the temporal muscle is broad but thin. Tissues of the scalp are thin, as if stretched. The scalp peels readily. The pericranium strips readily. The external surface of the bone is everywhere slightly roughened, hyperaemic and irregular. The parietal foramina are very large and deep; similar accessory foramina are present. The surface is irregularly mottled with pale yellowish areas and reddish areas of hyperaemia. The sutures are everywhere obliterated. Conformation of the calvarium is somewhat irregular, but the symmetry of the skull, as a whole, is maintained. The increase in size of the skull is symmetrical, the calvarium being greatly thickened. The dimensions of the skull following removal of the scalp, were as follows:

Greatest circumference.....	65.5	cm.
" diam. ant. post.....	23	"
Bi-parietal	18	"
Bi-malar	13.3	"
Naso-mental	14.2	"
Mento-coronal (length from the chin to the top of skull).....	26.5	"
Occipito-frontal	22	"
From zygoma to top of calvarium.....	12.7	"
Length of the nose.....	6.5	"
Distance from angle of jaw to symphysis menti.	6	"
Anterior fossa, greatest breadth (internally)...	10.5	"
Anterior fossa, ant.-post.....	6.3	"
Middle fossa, breadth.....	14.8	"
" " , ant.-post	5	"
Breadth of occipital fossa.....	12.5	"

The forehead is massive. The wings of the sphenoid are not thickened. The infundibulum of the pituitary is long and reddish in color. The Foramen Magnum is funnel-shaped, 2 cm. in breadth. The Clivus Blumenbachii is approximately 5.6 cm. in length 4.4 cm. in breadth. The pituitary gland measures 18 cm. by 12 mm. by 3 mm. Its right lobe is hemorrhagic. The gland is pale yellowish in color and rather firm.

The middle ears are normal. The sphenoidal sinuses are large. The mucous membrane is normal. The dura is adherent, especially on the right side, where it tears on stripping. It is everywhere thickened and the inner surface shows an extensive hemorrhagic membrane formation over the cerebral convexities. The pia is markedly oedematous and the Pachionian granulations are not prominent. A number of small opaque foci, the largest 2 to 3 mm. in diameter, are found in the pia over the vortex, near the longitudinal fissure. There is a considerable amount of blood stained fluid at the base. The brain, after the ventricles were opened, weighs 1440 gm. On the superior surface of the cerebellum there is fresh, reddish blood clot, and there is a considerable hemorrhagic infiltration in the pial meshes along the posterior border of the right lobe of the cerebellum. The vertebrals are markedly sclerotic. The basilar artery is very large, extremely sclerotic, with intense yellowish patches. The arteries of the Circle of Willis and the cerebral arteries are markedly sclerotic. The smaller vessels show extensive nodular sclerosis. The left lateral ventricle is filled with blood stained fluid. The right lateral ventricle containing reddish blood clot. There is an extensive hemorrhagic softening and infiltration involving the posterior and superior half of the lenticular nucleus, which extends into the optic thalamus and the adjacent wall of the third ventricle. The velum interpositum is infiltrated with blood and does not appear to be thickened. Otherwise the cross sections of the brain reveal no gross lesions.

The pineal gland measures 7 to 8 mm. laterally by 5.6 ant. post. The sella turcica is 28 mm. in breadth by 18 mm. ant. post. The clinoid processes are enlarged. The calvarium is soft, sawing through readily. The thickness of the occipital bone is 2 cm., that of the frontal bone 1.5 cm. The diploe are noticeable only in the occipital bone.

Lungs: The pleural cavities are free from fluid or adhesions with the exception that the left apex is slightly adherent. The pleurae of both lungs feel sticky. The right lung is slightly emphysematous, the surface being roughened and irregularly

mottled. An extra fissure, 2" in length by 1" in depth, is present in the lower lobe. The larger and smaller bronchi contain mucopurulent exudate and the mucous membrane is markedly congested. Section shows an extensive lobular pneumonia involving all lobes and more marked posteriorly. The left lung is rather voluminous; it does not feel heavy; is well aerated; the surface is smooth and on section shows nothing abnormal, with the exception of slight congestion. The pulmonary vessels are normal except for a few areas of intimal thickening. Bronchial lymph-nodes are small and anthracotic. There is no evidence of a tuberculous process either in the lungs or in the lymphnodes.

Heart: The pericardium is normal and contains a small amount of clear fluid. The heart is normal in size, the apex being formed by the left ventricle. The vessels are slightly tortuous and show a few areas of nodular sclerosis. The right auricle is normal. Fossa ovalis is normal in size. The foramen ovale is patent. Endocardium is slightly opaque. Tricuspid valve measures 13 cm. and is normal. There is no hypertrophy or dilatation on the right ventricle. The mitral ring shows a slight narrowing, the aortic segment being contracted and calcified at its base. The wall of the left ventricle measures 25 mm. in thickness; the musculature is pale brownish red in color and on section shows numerous small areas of fibrosis. The aortic cusps are slightly thickened and calcified at the line of their attachment; the line of closure is, however, normal. The portion of the aorta below the first part of the arch is the seat of a slight patchy sclerosis. The arch, thoracic and upper part of the abdominal aorta being normal. The branches of the abdominal aorta are only slightly sclerotic. The lower half of the abdominal aorta and the iliacs are somewhat broad but show only a slight sclerosis.

Spleen: Is small, rather firm, weighs 100 gm. and measures $10\frac{1}{2} \times 4\frac{1}{2} \times 4$ cm. On section it is congested and shows a slight increase in interstitial tissue.

Pancreas: Is about normal in size; lobulations are normal.

Liver: Weighs about 1600 gm. The serosa is normal and

pale brownish in color. The surface is smooth and on section the lobulations are indistinct, otherwise normal.

Gall Bladder: Is long and contains numerous facettèd stones, there is a very large number present. Common bile duct normal. Patency was not tested.

Adrenals: Left adrenal measures $5\frac{1}{2}$ cm. in length by $2\frac{1}{2}$ cm. in breadth. The right adrenal measures 6×4 cm. The organs are somewhat firm. The cortex is pale yellowish in color and measures 2 to 3 mm. in breadth. The medulla is dark red in color and shows a few patches of glistening tissue.

Kidneys: The right kidney 120 gm., left 160 gm. They are somewhat firm, apparently normal in size. The capsules are adherent in a few places. The surface is slightly granular. Signs of fetal lobulations persist. There are a few superficial scars on surface. The cortex is thickened and pale, the markings are distinct. The pelves, ureters and urinary bladder are normal. The prostate is large; otherwise normal. The testicles and epididymes are normal in size and appearance; there is a small hydrocele on left side.

Oesophagus: Shows a few distended veins in its upper half; otherwise normal.

Stomach: The mucous membrane is congested. There is a small, whitish area situated beneath the cardia of the mucous membrane (Lymphangioma).

Intestines: Small and large intestines contain a small amount of gas and hard fecal material. Appendix is normal. In the cœcum there is a small, reddish focus, 3×4 mm., which is freely moveable. There are several pale yellowish areas in the wall of the jejunum (Lymphangiomata). The mesentery is somewhat fatty. The lymph nodes are abundant but small.

Organs of Throat and Neck: The tongue is apparently normal in size. The lingual follicles are increased in size and number. There are a number of pale, elevated areas at the back and sides of the tongue, which on section show a milky fluid. The pharynx and larynx are normal. The tonsils are enlarged, the right showing a number of depressions filled with exudate.

The thyroid gland is somewhat symmetrically enlarged and pale reddish on section. The organ was not weighed. The parathyroid glands were removed.

The following measurements were made of the pelvis:

Intercristal	27	cm.
Interspinous	23.2	"
Internal conjugate.....	11.2	"
From the greater trochanter to plane of surface of foot.....	34.5	"
" ant. sup. spine to plane of surface of foot.....	37.4	"
Ant. sup. spine to bottom of external condyle of femur.....	19	"

The right knee joint is normal as to its articular surface and mucous membrane. The right femur is bowed. It is broad in its lower half and measures 18 cm. immediately above the condyles. On section the cortex measures 1 cm. in diameter. The diameter of the bone is 3.1 cm. The cortex of the left femur measures 6 mm. The diameter of the whole bone is 3.1 cm., right and left being of the same diameter. At a place above the middle of the right tibia, the thickness of the cortex is 1 cm. The bone is very firm, almost ebony-like. Vertebrae and marrow everywhere normal.

Ribs:. The marrow is red in color and normal in amount.

One of the earliest terms used in referring to diseases of bones is rickets. This term was used to include all diseases in which extensive bone changes occurred. Since then, groups of cases have been separated, such as Infantile Rickets, Achondroplasia, etc. The term Osteitis Deformans has long been used in connection with various diseases, which resulted in deformity of the affected bones. This term included constitutional diseases, fractures, and congenital deformities. The term was first used by Czerny in 1873 to describe a case of spontaneous curvature of the lower limbs. (This was in all probability a case of Osteomalacia.)

Sir James Paget who, in 1876, made use of the term Osteitis Deformans, in describing the condition which now bears his name, remarks in his original article: "Holding then the disease to be an inflammation of the bone, I would suggest that, for brief reference and for the present, it may be called after its most

striking character, osteitis deformans. A better name may be given when more is known of it."

Since that time various names have been applied to conditions apparently analogous to that described by Paget. To Paget's¹ original description, which appeared in the *Medico-Chirurgical Transactions*, 1876, little of note has been added. As he described it, the disease begins in middle life or later, progressing slowly during a period of many years, and causing no disturbances other than those due to mechanical changes in the diseased bones, those most often involved being the long bones of the lower extremity, the cranium, spine and clavicles. These enlarge and soften, and, owing to the pressure of the body and muscular traction, become curved and misshapen so that the statue steadily decreases. In a later communication, he states that there is not any clear evidence of general disturbance of health. In all cases, death has ensued through some coincident, not evidently associating disease, which has been aggravated by the condition of the bones, only in so far as they may have diminished the range of breathing and the general muscular activity. Paget correctly interpreted the condition as being a chronic inflammatory process.

Considered as a rather rare condition, Clopton, in 1906, collected seventy-five cases from the literature. Higbee³ and Ellis, in recording a case in the *Journal of Medical Research*, 1911, state that the number has been increased to 158 cases, 33 of which were noted in this country. The relative increase during the past few years points to one of two things—that the disease is becoming more prevalent or is more often recognized as such.

Numerous names have been applied to this condition, which illustrates the views of different authors, according to their interpretation of the process:

Osteitis deformans (Paget).

Pseudo-rachitis senilis.

Osteo-malacia chronica deformans hypertrophica.

Ostéite ossifiante diffuse (Lancereaux).

Osteolysis (Lobstein).

Hypertrophie spongieuse des os.

Craniosclérose.

Hyperostose généralisée.

Ostéite condensante.

Ostéomalacie hypertrophique bénigne (Vincent).

Pseudorachitisme senile.

Osteomyélite fibreuse.

Sclérose osseuse hypertrophique.

In reference to the etiology, little is known. In spite of the many theories that have been advanced, there is no generally accepted etiological factor. The most important are of interest, in that they tend to show the wide divergence of opinion.

Lesions of the nervous system, hereditary lues, arteriosclerosis, metabolic changes, and disturbances in secretion, particularly of the thyroparathyroid group, testicular, and suprarenal glands, have all been suggested as etiological factors.

Prince⁴ suggests, that it is not inconceivable that as degeneration of the anterior cornua may cause myopathies without other symptoms; so lesions of other special cell groups may cause osteopathies without other spinal symptoms. Curcio⁵ also suggests the possibility of a special trophic center in the gray matter of the spinal cord because the manifestations of the disease are usually symmetrical.

Syphilis: Some observers, particularly, Lannelongue⁶, regard the disease as a manifestation of congenital syphilis or a paralytic condition, asserting that improvement has been noticed following the administration of mixed treatment. Fournier⁷ agrees with Lannelongue and mentions the case of two brothers, one of whom presented a typical clinical picture of Paget's disease, the other showing marked evidence of congenital syphilis. He later speaks of the disease as a paralytic condition, to be classed with tabes dorsalis, general paresis, etc. Von Recklinghausen⁸ considers that the disease is not specific. Robin⁹ endeavored to differentiate Paget's from the luetic osteitis by comparison of the chemical composition of the bones, but his results

are of little value at present, as only one case was analyzed. Weber¹⁰ says that the osteitis deformans of congenital syphilis and Paget's may be differentiated as follows: 1. The youthful age of the patient in cases of congenital syphilis; 2. The relative absence of pain, which is almost constant in Paget's; 3. The favorable results obtained in syphilitic cases with proper treatment; 4. In syphilitic cases the tibiae are most severely affected, in Paget's disease the femora; 5. The presence of irregular bosses in congenital syphilis; 6. There is no evidence of any tendency for malignant tumors to supervene in the bones of syphilitic cases, as there is in Paget's.

Heredity: Several instances are recorded in which members of the same family have been afflicted with this disease. Chauffard¹¹ mentions mother and daughter; Smith¹², a father and son; Berger¹³, a mother and son. Paget, however, in reviewing 27 cases, remarked on the entire absence of any such history.

Occupation; Oettinger¹⁴ and Agasse Lafont noted that several cases had occurred among those whose occupation, such as bleachers, tanners and hatters, subjected them to the action of certain acids. They considered it possible that the chemicals may have some action on the osseous structure.

Arterio-Sclerosis; This condition is present so frequently that it may be considered almost constant. Not a few, particularly Béclère¹⁵, have considered that the interference with nutrition, resultant upon the sclerosis of the nutrient arteries of the bones affected, may have some etiological bearing.

Heitz¹⁶ and Hudelo speak of a woman 75 years of age, in which the skull was unchanged but whose femora and other bones presented lesions of Paget's disease. Arterio-sclerosis was not uniform. In this instance the arteries of the brain, skull and neck were normal, while those of the remaining viscera showed marked sclerosis, even to obliteration.

Interference with the function of the glands, and disturbance in the internal secretions has been considered. Our case is interesting in the entire absence of any change in the glands of

internal secretion, so far as determined. The lesions of the nervous system described in cases of Paget's disease should be accepted with considerable reserve. We believe this because of the pronounced arterio-sclerosis almost constantly associated with the disease, and because of the senile changes so frequent in brain and spinal cord, in old age. On account of the frequent association of arterio-sclerosis with the disease, it seems reasonable to suppose that it may act as a causative factor.

It is of interest to note that Max Koch¹⁷, before the German Pathological Society, demonstrated a case of Leontiasis ossium, and showed that the microscopical picture was similar to that occurring in Paget's disease. He therefore considers them identical.

We are unable to explain in detail how the vascular changes could so markedly alter the osseous tissues. That the process is evidently not always a generalized one leads us to suppose, that more consideration should be given to local disturbances, than to a general disturbance involving the osseous system as a whole.

Perhaps, as Higbee and Ellis state, accurate studies of the metabolism offer the most hopeful means of arriving at the proper solution of this question. Although we favor the idea that it is a local condition and not a systematic one, we realize that there must be some other causative factor present, for the reason that so many cases of marked cerebral arterio-sclerosis show no changes in the osseous system.

Microscopic examination of sections from our case show as follows:

Occiput; Section taken from the occiput—the outer table is formed of a thin layer of dense bone; there is little differentiation in structure of the bone. The inner table is very thin; the marrow spaces are large and everywhere filled with connective tissue composed of a homogeneous stroma and connective tissue cells with small spindle-shaped nuclei. The vessels are large; there is no proliferation of their endothelial cells. In places the connective tissue is more fibrous in character; the osseous trabeculae are large; there is well developed concentric lamellar

formation; the bone cells are small; there are few Howships lacunae and only in places are there osteoblasts. To be brief, the process may be described as an osteitis or osteomyelitis fibrosa; the trabeculae are large, well connected with each other, and there is everywhere evidence of a formative osteitis. The bone was extremely difficult to decalcify, and there is every evidence that there was no marked halisteresis.

Tibia: Section taken from the cortex of the tibia, which was thickened as above mentioned, shows very dense bone.

Right Femur: The cortex is formed of rather dense bone with large vascular marrow spaces, showing an osteogenic connective tissue very similar to that found in the occiput. Only a few giant cells are seen. The periosteum is thickened and fibrous; the inner layer is cellular.

Left Femur: The section taken at a level corresponding to that of the right femur is normal.

Vertebrae: Shows normal lymphatic marrow, in places quite fatty.

Ribs: The marrow spaces are very wide; trabeculae long and narrow.

Clavicle: Shows no noteworthy changes.

The gross lesions and the microscopic sections indicate that there has been an extensive formative osteitis of the calvarium, corresponding to what Von Recklinghausen has described as an osteitis fibrosa.

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DEMONSTRATION OF THE LESIONS PRODUCED IN THE APPENDIX BY OXYURIS AND TRICHOC- EPHALUS.

RUSSEL I. CECIL, M.D.

Dr. Cecil presented a series of lantern slides showing various phases of the invasion of the appendix by oxyuris vermicularis and trichocephalus dispar. He divided the cases into four groups as follows:

1. Those cases in which the appendix was the seat of catarrhal inflammation, but in which the worms had apparently remained inactive in the lumen of the appendix.

2. The cases in which the parasites had punctured or invaded the mucous membrane.

3. The cases in which the oxyuris had not only punctured the mucosa, but had produced more or less extensive ulceration of it.

4. The cases in which the appendix was gangrenous. In these no characteristic parasitic lesions could be demonstrated.

Dr. Cecil also demonstrated some healing oxyuris lesions—one of them consisting of a hyaline parasite completely encapsulated by fibrous tissue.

The trichocephalus lesions were shown to differ slightly from the oxyuris lesions. In the former the parasite tunnels along immediately beneath the epithelium, while in the latter the worm usually burrows into a lymph follicle.

In conclusion, Dr. Cecil said that in his series of 129 cases of appendicitis in children, 15% of them had been found to be associated with parasites, and that of these 70% showed specific parasitic lesions.

A CASE OF DISSECTING ANEURISM AND AORTITIS
DISSECANS.

J. GARDNER HOPKINS, M.D.

The specimen was obtained at autopsy on the body of a woman, fifty-four years of age. The clinical history was of little interest. The patient was admitted to the hospital with broncho-pneumonia, which followed a favorable course. Death was due to rupture of an aneurism into the left pleural cavity. At autopsy the hemorrhage was found to come from a large false aneurism lying between the pleura and the diaphragm. This opened into the aorta by a large gap measuring 5 cm. vertically by 1 cm. antero-posteriorly. The aneurismal sac extended 11 cm. from the aorta nearly to the lateral chest wall. The remnants of the arterial sac were found in the wall near the aorta, but elsewhere the sac was lined with fibrous tissue and nearly filled with dense lamellated thrombus. There was also a fusiform dilatation of the ascending portion of the aortic arch.

The lesion of chief interest, however, was a dissecting aneurism which lay in the left wall of the thoracic aorta. It was 13 cm. in length and 2 cm. in diameter. It communicated with the lumen of the aorta by a small opening, 11 cm. below the left subclavian. This opening just admitted a probe. The sac extended about 2 cm. above this point, ending blindly, and at an equal distance below was bifurcated, one neck communicating with the neck of the false aneurism previously mentioned. The other branch ended blindly about the level of the celiac axis. This branch was filled with a laminated thrombus. The wall of the dissecting aneurism was thick and nodular, in places reaching a thickness of 1.4 cm. The tissue was firm and fibrous, the lining for the most part smooth, but showing some areas of atheroma and calcification. The aorta showed extreme sclerosis. There were deep ulcerations of the intima separated by calcareous plaques with sharp edges. These changes were most marked in the abdominal aorta, but involved the entire vessel. The vessel wall was stiff and on section clefts were found in the sub-

stance. These were apparently preformed, though it is possible they resulted from trauma in section. If they were artifacts the tendency to form such clefts under slight stress was very marked. The other organs showed nothing of note.

Sections through the dissecting aneurism showed that it lay in the media of aorta inside the external elastic lamella. The elastic fibers of the media were fragmented and partly replaced by hyalin connective tissue infiltrated with round cells. The adventitia was very thick. The walls of the vasae vasorum were thickened by fibrous tissue and the endothelial cells were swollen. Some of the veins were entirely occluded by masses of leucocytes. The vessels were surrounded by collections of plasma cells and lymphocytes. Foci of these round cells were found elsewhere in the adventitia, but none of them contained giant cells or showed central necrosis. Spirochaetae could not be demonstrated in them by the Levaditi method. The picture was extremely suggestive of a gummatous process, but did not warrant an absolute diagnosis of syphilis. The intima of the aorta was thickened by atheromatous masses. Sections also showed areas of calcification in the intima. The inner wall of the dissecting aneurism showed similar atheromatous changes. The lumen was lined in part with a layer of flat cells resembling endothelium. Similar lesions were found in the abdominal aorta. The clefts in the wall found on cutting the vessels seemed to lie in the media inside the elastica externa, a position corresponding to that of the dissecting aneurism. The clefts were traversed diagonally by strands of unruptured fibers. Smaller clefts were found elsewhere in the media.

Changes of this type have been described from time to time in cases of dissecting aneurism, and Rokitsansky (*Lehrb. d. path. Anatomie*, 3d ed. II., p. 344) spoke of the possibility of their being the underlying cause of this peculiar lesion. He suggested two possible explanations of the lesion: first, that the freeing of the adventitia was primary, and the rupture of the media and intima secondary, due to loss of the support normally given by the adventitia; second, that the rupture might be primary and

the freeing of the adventitia secondary, if the disease impaired the elasticity of the media more than that of the adventitia.

Babes and Mironescu (*Beit. d. allg. Path. u. path. Anatomie*, 1910, xlviii, 221) have described a case of dissecting aneurism in which they found that the whole aorta had a tendency to split easily when cut, or contained preformed clefts in the wall. On section they found areas of hyaline degeneration in the intima and media and foci of round cell infiltration. They regarded this condition of the vessel, which they described as aortitis dissecans, to be the underlying cause of the dissecting aneurism.

A CASE OF OVARIAN PREGNANCY AND ONE OF TUBO-OVARIAN PREGNANCY.

J. GARDNER HOPKINS, M.D.

The specimen was obtained at operation on a patient of Dr. E. B. Cragin's at the Sloane Hospital for Women. The patient was a married woman, thirty-nine years of age, who had five children, the youngest being three years of age, and two miscarriages, the last two years before operation. The last menstruation occurred two months before operation. Without prodromal symptoms she was seized with sharp cramp-like pains in the lower portion of the abdomen, which lessened somewhat in intensity but continued until operation three days later. She had no bleeding and practically no other symptoms; her temperature was normal. Physical examination was negative except for tenderness, most marked on the left side. At operation two tumor masses were seen in the region of the left broad ligament. The tube on this side was normal; anterior to it was a thin-walled cyst, evidently parovarian, and posteriorly in the region of the ovary, a deep red mass adherent to the posterior wall of the Cul de Sac, which ruptured on removal, freeing a considerable mass of blood clot. The right ovary contained a few small cysts. The pelvic viscera were otherwise normal.

The specimen consisted of the left tube and the two cystic masses mentioned above.

The tube was 6 cm. long, 1 cm. diameter at the ampulla, very slightly convoluted, and not appreciably thickened. The fimbriated extremity was free and the fimbriae extended down a short distance over the surface of the parovarian cyst. The tube was not adherent to the ovary.

The parovarian cyst measured 6.5 x 4.5 x 5 cm. The wall was less than half a millimeter in thickness, and smooth, and showed two overlying systems of blood vessels. It was filled with clear fluid.

The ovarian sac was widely open when received. The blood clot which was found in it measured 6 x 5 x 3 cm. and was firm in consistence. The sac wall varied from 3 to 1 mm. in thickness, was opaque, and contained a few small cysts flattened out. The inner surface was rough and irregular and portions of the blood clot remained adherent to the wall. The sac was not attached to the tube, but was bound to the parovarian sac by a thick fibrous pedicle. The ovarian ligament was not definitely identified.

Sections were taken from all three structures. The tube appeared normal, showing no evidences of pregnancy.

The cyst had a thin fibrous wall and was lined by high cylindrical epithelium. The blood clot showed a few much degenerated chorionic villi. Other villi were found in portions of clot adherent to the sac. The remains of the fetus were not found. The sac wall showed typical ovarian stroma, the remains of a corpus fibrosum and of a few young follicles. Ovarian tissue was found in several portions of the wall. The lining of the sac was made up of dense fibrous tissue, poor in nuclei undergoing hyaline change. Large masses of this tissue were found in portions of the wall. It did not apparently represent an ovarian cyst.

This seems a definite case of ovarian pregnancy. While the condition has aroused considerable interest on account of its rarity, it was described by Erceres in 1614, but the diagnosis

in the early reported cases was not definitely established. In order to make a definite diagnosis it is generally considered that the specimen fulfil the requirements laid down by Spiegelburg in 1878: 1, the tube must be intact; 2, the fetal sac must be in position in the ovary; 3, the ovary must be connected with the uterus by the ovarian ligament; 4, ovarian tissue must be found in the sac wall. Williams has added the requirement that ovarian tissue must be found in several portions of the sac wall, and Norris that the tube must show no microscopical evidences of pregnancy. This case fulfils all the requirements except identification of the ovarian ligament.

There are probably many unreported cases of ovarian pregnancy and many reported cases may well have been true ovarian pregnancies, although the reports are too incomplete to establish the diagnosis. In 1909 Norris collected nineteen positive cases. I have been able to find three cases reported since then, all apparently positive; one reported by Lea in the *Journal of Obstetrics and Gynecology* for the British Empire in 1910; one by Rubin, published in the *American Journal of Obstetrics* for 1911; and the third by Young and Rhea in the *Boston Medical and Surgical Journal* for 1911.

The diagnosis is most easily made in early cases, of which this is an example. The diagnosis was, however, definitely established in a case of Ludwig's which ran to term, one twin being delivered from the uterus and another living twin from the ovarian pregnancy by laparotomy.

The symptoms are inconstant; there is frequently no bleeding, and in one case the patient had normal menstruation a few days before operation.

Much more common than true ovarian pregnancy are the so-called tubo-ovarian pregnancies in which the sac wall is composed partly of tube, partly of ovary. These may originate in one or two ways, either by rupture of a true ovarian pregnancy, or by rupture or abortion of a tubal pregnancy into a tubo-ovarian cyst. The second specimen is an example of the latter condition.

The clinical history of this case was of little interest. The patient complained of pain in the lower abdomen for the five weeks before operation and of profuse bloody discharge, which was increased by exercise. At operation a hematoma was found occupying the position of the right broad ligament, which ruptured on removal. The fetus was not found. The tube was densely adherent to the sac wall with which the fimbriated extremity was fused. The tube was unruptured, but there was blood clot in the ostium.

The section from the ampulla of the tube, which was filled with blood clot, showed well preserved chorionic villi in the lumen. The wall of the sac resembled in gross, ovarian tissue, and on section showed typical ovarian stroma with numerous follicles and a flattened-out corpus luteum cyst.

It seems fairly clear that this specimen represents the abortion of a tubal pregnancy into a tubo-ovarian cyst. The presence of villi in the tube seems to exclude the possibility that the pregnancy was primarily ovarian.

Discussion.

DR. JAMES EWING: Did not Dr. MacCallum present a specimen of ovarian pregnancy before this Society within a year or so? Of course, the careful distinctions between tubal gestation and ovarian gestation are of considerable interest. At the same time, if without requiring all the data, one includes the extra uterine gestations, which are largely ovarian, I think they amount up to a very considerable figure. And as such cases have very much the same significance, I think the impression that general ovarian pregnancy is a rarity is perhaps not well founded.

I have encountered cases which meet the requirements which Dr. Hopkins mentions, in that they were practically completely surrounded by ovarian tissue. But it is probable that many cases which pass as ovarian gestation are, or that border line which Dr. Hopkins so clearly defines.

DEFECTIVE DEVELOPMENT OF THE RIGHT LUNG,
DUE TO ANOMALOUS DEVELOPMENT OF THE
RIGHT PULMONARY ARTERY AND VEIN, AC-
COMPANIED BY DISLOCATION OF THE
HEART SIMULATING DEXTRO-
CARDIA.

E. A. PARK, M.D.

The subject of this report is a male child, two and one-half months old, admitted to the New York Foundling Hospital about two weeks before death occurred.

No history previous to admission is known.

The physical examination, in so far as it had bearing on the conditions found at autopsy, is as follows: A poorly nourished child. Color pale. Body normally formed. Chest symmetrical and moves with respiration alike on both sides. Abdomen has normal contour. The pulsation of the heart can be seen on the chest wall to the outer side of the right nipple in the fourth space and is fairly localized. It can be distinctly felt. Percussion shows dulness over a spot about the size of the normal heart situated in the lower part of the front of the right chest, separated from the right sternal margin by about $\frac{1}{2}$ cm. and not well defined above and to the right because of dullness of a somewhat different character. On auscultation the heart sounds are well heard over the front of the right side of the chest, but maximum at its lower part, at about the point of maximum pulsation. The sounds are normal, clear and unaccompanied by murmurs. The action is regular, but rapid. The left side of the chest in both front and back is very resonant, and the breath sounds are very intense and vesicular. Scattered subcrepitant rales are heard at the base behind. Over the normal site of the heart pulmonary resonance and vesicular murmurs are undiminished. Indeed, they both extend across the sternum to a point about 1 to 2 cm. beyond its right border. Over the right side of the chest, excluding that part of it where apparently the heart lies, the percussion note is

dull and the breath sounds are feeble, although in no place absent. Many subcrepitant rales, some of them having a consonating quality, are heard, more particularly over the lower parts than above. Fremitus is not obtained. But voice is more intense at the right base behind and in the axilla than on the left side.

The small intestine can be outlined through the thin abdominal wall and moves with respiration. The sigmoid, it is thought, can be felt in its usual situation.

The liver can be plainly felt extending 1 to 2 cm. below the costal margin. Its upper border percusses dull at the fourth interspace. The spleen cannot be felt. Both kidneys can be felt deep in the flanks.

In other respects the examination is normal.

The X-ray picture shows the heart to lie on the right side of the chest, separated 1 cm. from the right border of the sternum, and to be of normal size. The apex is directed to the left. The left lung seems to be entirely normal. The right lung apparently is consolidated in all but its upper part but the shadow of the upper part is not clear.

The clinical diagnosis was Lobular Pneumonia. Dextrocardia without rotation of the abdominal viscera. Marasmus.

The essential autopsy findings are these: The abdominal cavity presents a normal situs. The liver projects below the right costal margin a distance of $\frac{1}{2}$ cm. The stomach and coils of small intestine are somewhat distended. The spleen lies well back in the left flank. The diaphragm is intact and stands on the right side at the fourth interspace, on the left at the fifth rib. On opening the thorax the entire left side of the chest is occupied by the left lung, which extends also into the right chest about 2 cm. beyond the right border of the sternum. About two-thirds of the thoracic cavity are occupied by the left lung. The heart is seen well over to the right side, presenting by an opening between the lung margins about 3 by 4 cm. The right lung appears anteriorly only as a thin border to the right side of the heart.

On opening the pericardium, which is normal, and exposing the heart to view, the apex is found to be directed to the

left and formed by the left ventricle. Its anterior surface is entirely normal, except that the left auricle sends a finger-like process about $\frac{1}{2}$ cm. long forward across the pulmonary artery to rest on it and the adjacent part of the right auricle. The aorta is given off from the left ventricle, arches normally and gives its branches in the normal order and size. The pulmonary artery is given off from the right ventricle in normal position and is normally sized. The heart is certainly not enlarged. On further examination it is seen that the pulmonary artery divides normally into a right and left branch, but that the right is very small, not more than one-quarter the size of the left. Moreover, on dissecting clear the left auricle, it is found that two large veins enter it from the left lung, but no other pulmonary vein enters it at all. The right auricle receives inferior and superior vena cava in normal fashion. But no vein from the right lung can be traced to it or to the superior vena cava.

On opening the heart no abnormality is found in its interior.

The left pleural cavity is free from adhesions. As already stated, the left lung is very voluminous and composed of two lobes. Its color is yellowish gray: its pleural surface shining. It crepitates throughout and is normal on section. On examination of its hilus, bronchus, pulmonary and bronchial arteries and the two pulmonary veins can be identified and have normal relations.

The right pleural cavity contains adhesions. The lower half of the right lung is firmly attached to the chest wall. The lung is yet more firmly attached to the diaphragm, from which it is necessary to separate it by sharp dissection. On removal and examination of this lung it is found to be not more than one-half the size of the left and to be composed of three lobes. Its color is dark red; its consistency is firm, through some crepitation is found in its upper portion. To the moment of writing this lung has not been sectioned.

The hilus of this lung shows the cross section of a bronchus about the size of the left, of a thread-like bronchial artery, and a pulmonary artery, which, as already noted, is very small. No pulmonary veins are present at the hilus.

On examination of the under surface of this lung the cut ends of four arteries from 1 to 2 mm. in diameter are seen emerging from its surface. The other cut ends of the arteries are seen on the upper surface of the corresponding part of the diaphragm and can be traced as branches of a greatly enlarged phrenic. The blood supply of this lung, then, is obtained from the minute bronchial, the pulmonary of very small calibre, and the branches of the right phrenic artery piercing the diaphragm to enter its under surface. On separation of the upper and lower lobe of the lung a large vein is seen receiving branches from both lobes. It passes downwards between them to the under surface where its cut end appears. On examination of the upper surface of the diaphragm it could be traced emptying into the inferior vena cava immediately at its point of emergence from the diaphragm. This vein is not the right phrenic vein, for the latter can be identified as a delicate vessel terminating on the under surface of the diaphragm.

The abdominal viscera are essentially normal, with the exception of the liver, the upper surface of which is configured abnormally.

For the preparation of this specimen we are indebted to Dr. Schulte of the Department of Anatomy of the College of Physicians and Surgeons. Dr. Brown, who has been at work on the development of the pulmonary veins affords the following explanation:

The explanation of the anomaly is seen by reference to the embryology of the pulmonary vein. In a very early stage of the embryo of the domestic cat, represented by a length of 4.5 mm., the following condition of the venous system is found. Surrounding the entire length of the gut tube and existing also within its walls is a plexus of veins. This plexus communicates below with the omphalo-mesenteric veins passing in from the yolk sac. At this stage the heart presents an "S" curve which brings the venous chamber to the most cephalic and dorsal aspect of the organ. On either side of the venous chamber of the heart is seen a large afferent channel, the duct of Cuvier. The auricle

at this time is a single large chamber, presenting at its cephalo-dorsal angle the opening of the combined ducts of Cuvier forming the sinus venosus.

The plexus of veins around the gut tube above mentioned enters the auricular chamber by two taps, one situated cephalad and one ventrad to the opening of the sinus venosus, the other caudad and dorsad to that opening. At the point where the more cephalic tap leaves the ventral aspect of the gut there is a projection extending caudad which is the Anlage of the lung, and the plexus surrounding this projection, including the tap into the auricle, is the Anlage of the pulmonary system of veins. The tap spoken of as emptying caudad to the sinus venosus represents the future pars hepatica of the adult post cava.

It will be seen from the foregoing that the blood from the lung bud and the adjacent portion of the gut may select one of two routes to gain the auricular portion of the heart; first, directly through the pulmonary vein to the auricle, and secondly, by passage downwards to the level of the post caval tap and entering through it. In the normal development the septum transversum or diaphragm develops between the pulmonary and post-caval tap, and with this development a break takes place in a horizontal direction between the pulmonic venous return above and the post-caval return below, thus causing the blood from the lung to return to the heart by way of the pulmonary vein.

In this anomaly the break between the pulmonic and the post-caval systems has apparently occurred in a longitudinal direction, and the right pulmonary vein instead of passing inward and forward in its normal course to the left auricle, passes downward along the original embryonic communication on the left side, passing through the septum transversum and emptying into the post cava where that channel passes through the diaphragm.

Maud Abbott in her article on "Congenital Anomalies of the Heart," in Osler's System of Medicine, refers to cases of anomalies of the pulmonary veins, in which one or more emptied into the superior vena cava, or into the right auricle. But we have not been able to find a case in which the pulmonary vein emptied into the inferior vena cava.

Eppinger¹ reports a case in which a maldeveloped part of the right lung was supplied by the phrenic artery, which penetrated the diaphragm to accomplish it. But more than four pulmonary veins he found entering the left auricle.

Displacements of the heart, due to defective development of the lungs, are not very infrequent, and when the defective lung is on the right side, may simulate dextro-cardia. The other lung undergoes a compensatory hypertrophy. But such cases are not dextro-cardia.

Dextro-cardia, without situs inversus, has been recently studied by Nagel². His series of six cases, which were proven at autopsy, had certain characteristics in common, one of which was the direction of the apex to the right, shown not to obtain in our case by the X-ray. All six presented defects in pulmonary artery and ventricular septum.

In our case the defective development of the lung seems most likely to be extra-uterine in the time of its occurrence and due to the deficient blood supply from the right pulmonary artery. The phrenic branches represent probably a compensatory means of blood supply. That the defect in development which caused the vein playing the role of pulmonary vein to empty into the inferior cava could also have resulted in an adherence of lung to diaphragm and so have afforded a means of entrance of the phrenic vessels into the lung, seems probable.

What the pleural relations to the phrenic vessels were could not be determined. In Eppinger's case the pleural investment was by a continuation of the ligamentum latum pulmonis. But in the subject of this report adhesions between parietal and visceral pleura about the lower part of the right lung were so extensive as to make such a determination impossible. These adhesions indicated an inflammatory condition in the right lung, probably extra-uterine. Light can be thrown on this by histological study of the right lung.

This case will be reported more fully elsewhere.

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AN INFECTIOUS ENDOCARDITIS FOLLOWING MEASLES IN A CHILD AGED TWO AND ONE-HALF YEARS.

E. A. PARK, M.D.

The clinical history of this case is substantially as follows:

Previous to the present illness, the child had been well and had no acute diseases of any kind. The present illness began with an attack of measles, which was part of an epidemic of measles then present at the New York Foundling Hospital. In company with several other children, this child developed Koplik spots, catarrhal symptoms, fever, and a macular eruption which was regarded as being fairly typical. In addition to the house staff, the case was seen by Dr. Rowland G. Freeman and Dr. Matthias Nicol, both of whom concurred in the diagnosis of measles. With the measles the child developed pneumonia and seemed very sick. The eruption differed from that of the other children in that it was slower in reaching its full development and became what was termed "hemorrhagic," although at autopsy no evidence of diffuse hemorrhages into the skin were present. Four or five days after the eruption was first noted, nine days after onset, the temperature, which had been elevated at 103° to 104° , began to assume a septic type, ranging from 105° to normal. The child seemed to be very sick and died about fourteen days after the beginning of the illness. The clinical diagnosis was measles, complicated by broncho-pneumonia.

The autopsy was performed by Dr. Pappenheimer. An abstract of his protocol is as follows:

Anatomical diagnosis.—Acute infective endocarditis of the mitral valve. Lobular pneumonia. Acute hemorrhagic nephritis with infarcts. Infarcts of spleen. Multiple focal necroses of liver. Double suppurative otitis media. Necroses of heart muscle. Petechial hemorrhages of skin and mucous membranes.

External examination. The body is that of a well nourished child weighing about 30 pounds. Length 88 cm. Head circumference 46 cm. Chest measurement 42 cm. Sterno-public meas-

urement 29 cm. Rigor mortis is present in all the extremities. The skin and visible mucous membranes are pale. There are a few dull purplish areas over the upper part of the abdomen, the thighs and the arms. There is marked hypostasis. Over the entire back the skin is desquamating in the form of fine scales.

Examination in situ.—The subcutaneous fat measures about 1 cm. over the abdomen. The omentum is free and contains a little fat. It overhangs the somewhat contracted small intestine. The appendix overhangs the pelvic brim in the right iliac fossa and has a short mesentery. There are very numerous hemorrhagic lymph nodes in the mesocolon and in the mesentery itself and along its root. These vary in size from 1 mm. or less, to 2 cm., are brilliant red in color and especially numerous along the attachment of the mesentery to the transverse and descending colons. The diaphragm stands on the right at the 5th interspace, on the left at the 4th rib. The spleen does not reach to the free border of the ribs and lies in the mid-axillary line. The peritoneum is smooth and glistening.

Thorax.—The pleural cavities are free from fluid. There is a single fine fibrous adhesion between the lower border of the left lower lobe and the parietes. The pericardium contains a few cubic centimeters of clear yellowish fluid.

Thymus.—Consists of a rather dense structure. Weight, 4 gm. The tissue about is somewhat oedematous. On section the lobules are rather indistinct and of a grayish yellow color. The glandular substance is atrophic.

Lungs.—The left lung is voluminous, especially the upper lobe, the anterior portion of which is exceedingly pale with emphysematous vesicles. The lower lobe is darker in color but somewhat mottled, there being depressed purplish areas alternating with more prominent light lobulations. The pleurae are shining but sprinkled posteriorly with small bright red petechiae. The bronchi are hyperaemic and some of them filled with yellow purulent exudate. The lymph nodes at the hilus, up to 1 cm. in size, are hyperaemic, succulent and without pigmentation. On section the upper lobe is air containing, except for the tongue

shaped lower anterior portion, which is completely collapsed and presents a pale, smooth, airless surface on section. The lower lobe is much more hyperaemic. On section it shows extensive areas of consolidation, which are quite prominent above the aerated portion. They are granular and mottled grayish red and permit little exudate to be scraped off. These areas occupy large more or less wedge shaped areas at the extreme base of the lower lobe and show more or less distinct peribronchial distribution. In places the pneumonic process seems to have gone on to the formation of small abscesses filled with thick creamy pus.

The right lung superficially resembles the left. The anterior portions are extremely pale and emphysematous, the posterior dark purplish, with light areas somewhat depressed, below the level. On the posterior surface there is a fine fibrinous exudate. Numerous petechial hemorrhages are scattered over the pleura. On section areas of lobular consolidation resembling those on the other side are present in both upper and lower lobes, occupying the posterior half of the upper, and the greater portion of the lower lobe. There are also a few inconspicuous areas in the middle lobe. All of the bronchi are filled with a thick purulent exudate.

Heart.—Normal in size. Weight, 64 gm. The epicardial fat is scant in amount. The epicardium is smooth and glistening. The heart muscle, as seen from the outside, is pale and dotted here and there with small hemorrhagic spots 1 to 2 mm. in size and small grayish yellow areas of opacity which are apparently not related to the hemorrhages. The right auricle contains a pale chicken-fat clot. The foramen ovale admits a fine probe. The tricuspid valves and pulmonary cusps are normal. The right ventricle measures $2\frac{1}{2}$ mm. in thickness. It is rather moist and swollen. The left auricle is normal. The mitral valves are the seat of fresh thrombotic papillary vegetations, which are situated near the margins of the valves and extend down along the margins of the chordae tendinae as far as the apices of the papillary muscles. These vegetations are gray and very friable and soft and but loosely attached to the underlying valves. On tearing

them off, they leave a slightly roughened endocardium. The mitral valves themselves are rather thick and dilated, the parietal musculature is flattened. The ventricle measures about 5 cm. in length. The endocardium over the septum shows a somewhat streaky opacity, and shining through are seen irregular opaque yellow spots similar to those described on the surface. The muscle of the ventricle is about 9 mm. in thickness. It is pale and moist and on section shows sharply circumscribed dull yellow gray patches, one of which in the upper portion of the ventricle extends through the wall. The aortic valves are normal. The aorta measures 33 mm. over the sinuses.

Spleen.—Weight, 20 gms. Measurements, 7 x 4 x 2½ cm. Capsule smooth and tense. The surface is rather mottled with dark purplish and paler grayish red areas. Near the upper pole there is a pale gray sharply circumscribed area 3 by 8 mm., surrounded by a hyperaemic zone, obviously a small anemic infarct. On section the splenic pulp is rather pale, very firm and smooth and mottled with dark hemorrhages. The follicles are quite numerous but very small. The trabeculae are more in evidence than ordinarily.

Liver.—Weight, 365 gms. Measurements, 15 x 10 x 5 cm. The surface is smooth, the lower border sharply defined. Seen through the surface of the right lobe are more or less sharply circumscribed areas, in which the center of the lobule appears to be represented by opaque yellow spots less than 2 mm. in diameter, about which the liver tissue seems gray and translucent. The margins of these areas are somewhat hyperaemic. On section the same appearance is distinctly seen. The yellow portions lie around a very translucent gray tissue without other lobular markings. There are also minute punctate hemorrhagic spots in the parenchyma.

Adrenals.—Each weighs 3 gms. Normal.

Kidneys.—The capsule is easily peeled. The surface is smooth but profusely sprinkled with larger and smaller hemorrhagic areas. These range from barely visible punctae to larger blotches several mm. in size. There can also be distinguished

against the yellowish background minute yellow points, and slightly more prominent circumscribed grayish yellow areas, the largest of which in the right kidney, is 1 to 2 mm. in diameter and surrounded by a hyperaemic zone. On section the renal tissue is extremely soft and moist and bulges above the surface of the capsule. The general color is pale grayish pink, but it is profusely blotched with smaller and lighter hemorrhages. Some of these are present also in the pyramids, although they are chiefly confined to the cortex. The glomeruli are extremely prominent. Many of them are surrounded by a zone of hemorrhage. This condition is confirmed by inspection with a hand lens. Pale areas on the surface extend a variable distance into the cortex as wedge-shaped necrotic pale grayish yellow areas with a yellow border. The pelves are free from hemorrhages. The mucosa is normal. The ureters are normal.

Bladder normal.

Uterus and appendages normal.

Tongue normal.

Pharyngeal lymphadenoid tissue seems rather hyperplastic and there are a few minute hemorrhages.

Tonsils normal.

Stomach.—Contains brown shreds mixed with mucous. The mucous membrane is pale and dotted with pink petechiae.

Intestine.—Contains a small amount of unformed fecal matter. The Peyer's patches are somewhat hyperaemic, but not prominent. The solitary follicles are inconspicuous both in the small and large gut. The mesenteric lymph nodes are quite numerous and of a bright red color. Section through some of the larger ones show grayish opaque areas of necrosis.

Pancreas normal.

Bones.—The epiphyseal lines are normal.

Brain.—The calvarium and dura mater are normal. The cortical vessels are engorged with blood. The brain tissue on section is hyperaemic. The cortex is purplish blue and the blood punctae numerous. The ventricles are normal.

Middle ears.—On both sides they show marked congestion

of the mucous membranes, the cavities being filled with thick greenish pus.

The microscopical examination was as follows:

Myocardium.—The muscle fibers appear somewhat vacuolated. The striations are very indistinct. The nuclei are small and pycnotic. Definite areas of necrosis, however, and inflammatory changes are not evident in the section. One of the larger veins is plugged by a large hyaline thrombus.

Thyroid normal.

Pancreas normal.

Tonsils.—In one of the crypts the epithelium, which is elsewhere normal, shows ulcerations, the lymphoid tissue being covered by a necrotic exudate. Scattered through the otherwise normal lymphoid tissue there are a few inflammatory foci surrounded by fibroblasts and containing nuclear detritus and bacteria.

Lymph nodes.—Many of the lymphoid cells are pycnotic; some of the vessels containing hyaline thrombi. Some of the nuclear fragments are taken up by phagocytes. There are acute degenerative changes.

Liver.—The central portions of the lobules are composed of liver cells showing varying degrees of fatty infiltration. The nuclei are well stained and there is no evidence of necrosis.

Hypophysis.—Hyperaemic. The oxyphilic cells predominate. The pars nervosa is normal.

Adrenal.—Normal.

Brain.—Section through the cortex shows normal nerve cells.

Kidney.—The section shows an anemic infarct, evidently recent since the glomerular and vascular structure is still present in places. There is marked leucocytic invasion between the necrotic tubules. At the margin of the infarct the vessels are distended with blood. In the intact portion of the kidney the convoluted tubules are dilated with low flattened epithelium. Many of the Henle tubules contain hyaline or waxy casts. The interstitial tissue is oedematous but not increased in amount. The glomeruli are apparently normal.

Lungs.—The alveoli throughout, save for a small area, are filled with an exudate composed almost wholly of polymorphonucleated leucocytes in a rather dense fibrinous plug. There has been destruction of the alveolar septa with the formation of small abscesses. The bronchi are filled with a purulent exudate, the epithelium being well preserved. In places there is a little fresh fibrinous deposit on the pleura.

No bacteriological report was made.

Infectious endocarditis in young children is very rare. Heubner reports a case of infectious endocarditis in an infant of ten months old. He speaks of the rare association of an infectious endocarditis with the virulent form of measles in which the blood culture often shows the presence of streptococci.

This case is presented not because it differs in any respect from the majority of cases of infectious endocarditis, but because of its occurrence at so early a period of life, and it is also of interest because of occurring in the course of measles.

PRESENTATION OF SPECIMENS.

D. FELBERBAUM, M.D.

Papillary Adenoma of Kidney.—The first case is a specimen removed from an individual who was about sixty years of age and who had a very extensive and extreme form of chronic articular gout. Besides this, he had an immense abdominal tumor, filling up the entire left half of the abdominal cavity. While he was an inmate of the Montefiore home, he had numerous attacks of severe hematuria. He died rather suddenly this year. At autopsy, this large tumor was found, weighing almost fourteen pounds, with extensive metastatic nodules throughout both lungs and one large tumor mass in the right lobe of the liver. At first, from the gross specimen it was thought to be a hypernephroma; it was very yellowish and quite broken

down. On subsequent examination, it proved to be a papillary adenoma of the kidney. Sections from the primary tumor and from the metastases showed the same structure.

Unusual Form of Liver Tuberculosis.—The next specimen is a rather unusual form of tuberculosis in the liver, in which the tuberculous deposits take on a large nodular form. This man was 52 years old, and was admitted to the Montefiore Home on May 8, 1907. His history dated back eleven months prior to admission, when he first complained of severe abdominal pain. He had never had blood in the stools, diarrhoea or jaundice, but was considerably emaciated, and presented large lymph-nodes. The liver felt smooth and hard on palpation. In August, 1907, the nodes in the left groin suppurated, the discharge continuing for a year when it ceased spontaneously. He began to gain weight until the early part of December, 1910, when he developed a cough, hectic temperature, and again rapidly emaciated. Numerous blood counts showed degeneration of the red cells. A gastric analysis was negative.

At autopsy, there were found many old tuberculous retro-peritoneal lymph-nodes. The stomach was normal. The liver was studded throughout with irregular masses, varying in size. These were sharply outlined from the liver tissue, and showed a depression on the surface. There were a few areas of hemorrhage in the liver substance. The kidneys showed parenchymatous degeneration.

On microscopic examination, the nodular masses, which were at first thought to be cancers, were found to be formed by conglomerate tubercles, surrounded by areas of round cell infiltration and many giant cells. Tubercle bacilli could be demonstrated.

Spontaneous Rupture of the Heart.—The next specimen is a case of spontaneous rupture of the heart. The subject died May 7, 1906. He was an inmate of the Montefiore Home for ten years, with cerebro-spinal spastic paralysis. Death occurred suddenly. The pericardial sac was found to be distended with recent blood clot and about 500 cc. of fluid blood. The left ven-

tricle showed along the line of the coronary artery, a tear one and one-half inches in length. The edges of the tear were ragged and the adjacent tissue rather spongy. Dr. Harlow Brooks found on making sections that the tissue about the tear showed gummatous infiltration and a great deal of degenerated material through which the rupture had taken place.

Discussion.

DR. EWING: I was partly responsible for the mistaken diagnosis in the first case. This was quite a remarkable tumor and as we are accustomed to remarkable conditions at the Montefiore Home, I thought it was quite in line that we should have a curious hypernephroma.

However, it proved to be quite different in that it perfectly preserved the shape of the kidney, whereas hypernephromas, after reaching a certain dimension, are apt to be rather irregular in shape. On gross section of this enormous tumor the separation of renal substance from the tumor was not so sharp as is usual in hypernephroma. On the other hand, the general appearance of the gross section strongly recalled what one is accustomed to see in hypernephroma. The large blood content, cysts filled with blood, highly pigmented yellowish areas, and the general conformation, strongly recalled hypernephroma.

On microscopical section we find something entirely different. In view of the present discussion as to the origin of hypernephroma, it seems to me that we have here a standard on which we may proceed with the discussion of the renal origin of various tumors differently interpreted by different authors. For here is a renal tumor with structure having no resemblance whatever to the ordinary hypernephroma, and evidently derived from the kidney tissue.

NERVE FIBRILS IN THE SINO-AURICULAR NODE.*

B. S. OPPENHEIMER AND ADELE OPPENHEIMER.

Although several observers (Wilson,¹ DeWitt,² Engel³) have succeeded in staining the nervous elements (fibers, fibrils and ganglion cells) in the *auriculo-ventricular* system of the heart, no one has thus far described all these structures in the *sino-auricular* node. Wilson was the first to demonstrate by means of a vital stain, not only the nerve-fibers accompanying the bundle of His, but also ganglion cells of various types and a rich plexus of nerve-fibrils intimately related to the specialized musculature of the conducting system. The bundle of His may therefore be considered anatomically a neuro-muscular structure. As the region of the sino-auricular node of Keith and Flack is now believed to be the pacemaker of the mammalian heart, we have thought it of importance to make a similar investigation of its nervous elements.

Subepicardial nervous elements overlying the sino-auricular node may be readily demonstrated with the ordinary van Gieson stain. As is known, there occurs here *over* the node a rich collection of ganglia and nerve fibers; and in the literature there is even an occasional mention of a nerve fiber or ganglion cell *within* the limits of the node (W. Koch⁴, Schwartz⁵). But no one thus far has used a specialized nerve stain for the Keith-Flack node and consequently there has been no description whatever of nerve-fibrils.

We employed a vital stain of methylene blue, following for the Keith-Flack node the same technique as Wilson applied to the bundle of His. We report at this time only the results of using this method on the hearts of freshly killed pigs, bullocks and sheep, although the hearts of several other animals are being investigated.

In the pig, sheep and bullock, we found a plexus of nerve-fibrils in the sino-auricular node such as Wilson described for

*Presented at the January meeting; manuscript received too late for publication in Vol. XII, Nos. 1 and 2.

the auriculo-ventricular system. Fine fibrils with varicosities were seen intimately interwoven with the specialized musculature of the Keith-Flack node, and were also seen surrounding the special nutrient artery of the node. Such fibrils were identical in appearance with those which composed the nerve-fibers. In certain sections nerve branches from the subepicardial nervous structures seemed to penetrate the node.

In the pig's heart, there occurred in addition to these nerve-fibrils a multipolar ganglionic cell.

Aside from the subepicardial nervous elements, the sino-auricular node, therefore, contains *within* its limits, nerve-fibers and nerve-fibrils.

Sections showing nerve-fibrils in the sino-auricular node of the pig and bullock were demonstrated under the microscope, and a drawing presented.

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METASTATIC HYPERNEPHROMA OF THE LUNGS.

B. S. OPPENHEIMER, M.D.

By way of comparison with Dr. Felberbaum's case of papillary adenoma of the kidney with lung metastases, I should like to present a case of metastatic hypernephroma in the lung.

The patient from whom this specimen was obtained was a woman who was 57 years old at the time of her admission to Monette Home in June, 1910. She died March 15th, 1912.

The history in brief was as follows:

In 1906 she had an abdominal operation performed in

London, at which the left kidney must have been removed. In spite of several attempts it has been impossible to learn the nature of the kidney lesion at the time of this operation.

In 1908 she had a sudden attack of unconsciousness followed by paralysis of the left half of her body. After a stay at two of the New York hospitals, she was admitted to the Home as a case of hemiplegia.

At the time of her admission, physical examination did not reveal anything abnormal in her lungs. The radial arteries were markedly thickened. She had a left-sided hemiplegia with hemianopsia.

Toward the end of the year 1910, she began getting pulmonary signs and symptoms. Dr. Harlow Brooks was the first to suspect metastatic tumor of the lung. An X-ray of the chest taken at his suggestion was a decided help in revealing the presence of a growth in the left chest.

On March 17th, 1911, patient coughed up bloody sputum.

By October, 1911, the physical examination of the chest revealed an area of dulness on the left side with diminished voice and fremitus from the fourth rib down.

December, 1911, a marked distention of the veins of the axilla and chest was noted on both sides, more marked on the right than on the left. The thoracic wall showed several hard, thickened, tortuous arteries.

The patient became gradually more cachectic.

In February of the year 1912, exploratory aspiration of the right pleural cavity withdrew one ounce of bloody fluid which did not show tumor cells.

March 9th, 1912, patient was extremely emaciated and was coughing up large quantities of thick, purulent sputum without blood. The heart was apparently displaced to the left, with the apex beat at the anterior axillary line. There was a moderate oedema of the upper portion of the thighs, of the feet, and of the ankles. There were no bone metastases.

Patient died March 15th, 1912; that is about six years after the nephrectomy.

At autopsy the right lung was found to be very adherent and studded with numerous white nodules, varying in size from that of a pea to that of an olive. At the root was one as large as a small orange which had become degenerated and filled with a grumous material.

The left lung, the one here presented, shows one large inter-lobar tumor about the size of a hen's egg. This tumor was undoubtedly the one revealed by X-ray. It has a necrotic centre. In addition there are numerous smaller nodules, chiefly pleural or sub-pleural. These are firm, white, usually flattened, well circumscribed. The borders of the lung, especially the inferior border, have short fringes of tumor tissue.

The only remaining, that is the right kidney, showed a solitary cortical nodule which on microscopic examination presented the same histological structure as the tumors in the lung.

Microscopic examination showed that the tumor evidently belongs to the hypernephroma group although morphologically it is not a typical hypernephroma. Its peculiarity consists in the presence of numerous giant cells. With Sudan III fat could be demonstrated in the endothelial and tumor cells, and with the polarizing microscope Dr. Hanes proved the presence of anisotropic fat globules. The histological picture of hypernephroma is very variable as has been pointed out by Hall who studied a series of seventeen cases.

The question of the origin of renal hypernephromata from heterotopic adrenal tissue in the kidney is still under discussion. In a recent paper Glynn agrees with Stoerk, Zehbe, and Wilson and Willis, who contend that renal hypernephromata seldom if ever arises from adrenal rests. They believe, in one way or another, in the nephrogenic origin of the renal hypernephromata.

Discussion.

DR. EWING: I had an opportunity to look at the sections of the metastatic hypernephroma of the lungs, and I think it is worth noting that they present an unusual picture for hypernephroma. All or most of the pulmonary nodules present many large giant cells and if one has not seen this particular picture, it will enlarge his knowledge as to the remarkable forms these tumors may take.

EARLY OVUM IN A FALLOPIAN TUBE.

I. RUBIN, M.D.

An exceedingly early ectopic ovum.—This specimen, of which I shall show sections on the screen, was removed from a patient at Beth Israel Hospital in September, 1911. The patient was admitted to Dr. Bandler's service with symptoms of pain in the right side of the abdomen and hemorrhage. She was 23 years old, had been married two months, and began to show symptoms two weeks after her last regular menses, i. e.: five days before admission. Two days later, in addition to the cramp-like pains in the abdomen, she also noticed hemorrhage. On examination we found the uterus slightly enlarged and to the right side was a fairly movable mass of firm consistence. There was no blood at the time of this examination. The tentative diagnosis of ectopic gestation was made; a preliminary curettage was then done for diagnostic purposes. The curetings, however, did not point to intra-uterine pregnancy, but, in view of the clinical history, Dr. Bandler deemed it advisable to open the abdomen. There was no blood, either free or clotted, anywhere in the peritoneal cavity. On the right side, however, the ovary was seen to be twice as large as compared with the left ovary, and contained a large hemorrhagic mass. The latter resembled a hemorrhagic corpus luteum. At the same time ovarian pregnancy had to be thought of. The right ovary and the greater portion of the right tube were removed en masse. A small portion—about $\frac{3}{4}$ of an inch in length—of the isthmic tube was left in situ. A hasty examination of the excised portion of the tube showed that a few drops of blood could be expressed from the fimbriated end. In view of this finding, and also to complete the anatomical study to prove an ovarian pregnancy, should this latter be the case, I thought it advisable to resect the residual portion of the tube, to which Dr. Bandler readily consented. I was surprised to find, on rolling this isthmic portion of the tube between my fingers, a small nodule of the size of a very small pea. The sensation was so curious and so suggestive that I asked several gentlemen to palpate it. I fear the specimen must have suffered as a result of this manipulation.

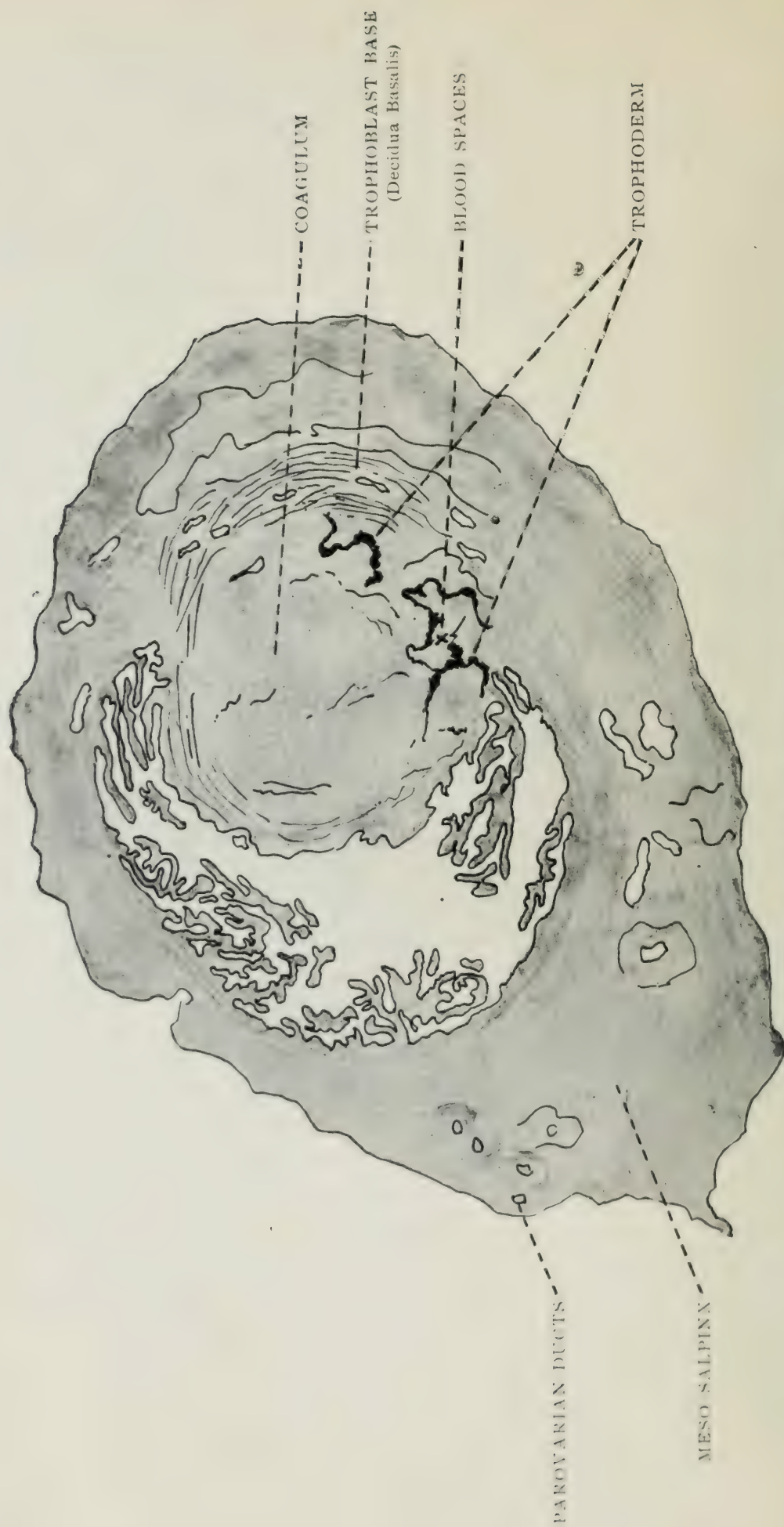


FIG. 1. DISTAL HALF (x 15 DIAMETERS) — CROSS-SECTION



FIG. II. PROXIMAL HALF (x 15 DIAMETERS) — CROSS-SECTION
Camera Drawing

Demonstration of the Sections.

The nodular portion of the tube was divided at about its middle point after hardening. It showed a rather firm coagulum attached to one wall, resembling the picture of an ectopic mass on section. Either half of this nodule was then blocked and cut serially. Unfortunately a number of sections were thus lost; the series, however, shows a very clear picture of an exceedingly young ovum in the tube. The distal half shows a coagulum attached to the superior wall of the Fallopian tube and occupying about one half the width of the tube. Only one third of its circumference is attached. It measures at its greatest diameters $3 \times 3.5 \times 3.75$ millimetres. The tube is apparently not enlarged and would correspond to an average tube at this point, i. e., 5×6 millimetres. At the base of the coagulum are seen two masses of trophoderm, from which are given off several streaks of trophoblast, which stretch toward the outer and the inner portion of the ovum and enclose between them fresh blood cells. The ovum itself is intimately connected with the muscularis, its base rests upon several layers of large pale and more intensely stained fusiform and large polymorphous cells, which form the decidua basalis. The circumference of the coagulum is lined by one or two layers of the same sort of cells, which may be taken to represent the decidua reflexa. These cells, however, are in a very poor state of preservation. Here and there throughout the coagulum may be seen small clusters of trophoblast cells. The embryo as such can, however, not be made out. The tubal epithelium fringes the margin of the ovum a little above its point of insertion on either side. The few adjoining tufts show a varying number of decidua cells. The musculature also shows a small number of these wandering decidua cells close to the base of the ovum. There is a small amount of leucocytic infiltration immediately underlying the base of the ovum, *but this is conspicuously absent in all the other elements of the tube.* The ovum gets smaller and smaller as we approach the fimbriated end, and is finally seen to consist of a small blood clot in connection with

one column of the tubal epithelium and then to disappear altogether. The tube itself beyond this point shows nothing abnormal.

Followed toward the uterine end of the tube, the trophoderm quickly disappears; instead there is only the trophoblast capsule with well marked decidua basalis. At this point there is pronounced hypertrophy of the muscle. A great number of muscle fibres are seen to penetrate the coagulum. The margin of the latter is almost completely enclosed by a single layer of tubal epithelium. The entire coagulum is much smaller than that of the other half, as above described, and fills only a small portion of the tube lumen. But here we also encounter another smaller lumen in the vicinity of the broad ligament. This lumen is lined by columnar epithelium, which is thrown into very primitive tufts, and resembles in general the histologic picture of the isthmic portion of the tube. A broad muscular septum separates these two lumina. As we follow this series toward the uterine end, these two lumina show a variation in size, so that soon they are of equal width when there begin to appear small channels at the same side of the insertion of the ovum lined by tubal epithelium, which connect the two. Presently the septum gets thinner and smaller, the two lumina communicate broadly, the ovum almost disappears, while its muscular bed is very conspicuous. The septum itself disappears entirely and is only represented by a local thickening of the muscularis. The tube beyond this point shows nothing exceptional.

This brings us, I think, to the question of etiology of ectopic gestation. Explanations so far are numerous, and by no means altogether established. The difficulty in the study of the etiology of ectopic gestation lies in the fact that material dealing with the very early stages has been exceedingly scarce. We have even come upon our case quite by accident, although clinically the presumptive diagnosis of ectopic gestation was justified. Ectopic gestations as ordinarily studied for purposes of pathogenesis already show a certain amount of intra-capsular or extra-capsular hemorrhage, and a certain amount of inflammation. The inflammation may be secondary to the ectopic as well as a primary cause

of the same. It is desirable, therefore, to have an ovum which had not proceeded to this stage. Our specimen shows a complete absence of inflammatory changes. Instead we find a muscular spur at a portion of the tube where the lumen is ordinarily narrow. It would seem that the ovum, in traveling toward the uterine end of the tube, had encountered this spur, which acted in a purely mechanical way, and then penetrated the mucosa and embedded itself into the hypertrophied portion of the muscularis. Whether this was intra-columnar or columnar is rather hard to say. The muscular spur, in conjunction with the local muscular hypertrophy would serve as a direct obstructing cause. The small diverticulum which dips down toward the mesosalpinx is situated toward the proximal side of the septum, and hence cannot be considered as a factor in the etiology of this ectopic gestation. The condition is rather one which resembles the inter-muscular division of the tubal epithelium, as first described by Werth and Futh, and also the partial attempt at a duplication of the tube, as described by Goebel. I think that in this case we might reasonably say that the cause of the lodgment of the ovum in the tube is purely a mechanical one, and was due to an anomalous overgrowth of the musculature, plus a muscular septum formation, which together narrowed the normally small lumen at the isthmic portion of the tube and rendered impossible the progress of the ovum toward its normal goal—the uterus.

Discussion.

DR. STEWART: Might it not be possible that there is another explanation for the thickening of the muscle coat around the ovum. Is it not true that when the ovum grows in the tube there is a hypertrophy of the tubal musculature, just exactly as you get in the uterus? This muscular enlargement might therefore be more the result of the tubal implanation, than its cause.

DR. EWING: I would like to ask if any villi were found in gestation.

DR. RUBIN: I think that it is rather likely that the hypertrophy of the musculature may have followed the lodgment of

the ovum, except that this would not account for the septum formation at the same time. Nor would such hypertrophy be so peculiarly eccentric.

There were no chorionic villi found. The ovum itself is exceedingly young, I think. As far as I have been able to see, it is probably the youngest ovum in a tube that has been demonstrated. That shown by Futh in 1899 was supposed to be two weeks old but it was very much larger than the one shown in my specimen, and in the light of most recent investigations, notably those of Teacher and Bryce, must have been much older than was originally estimated. My specimen, though much larger than Leopold's ovum in utero shows almost identical pictures. Though it is not possible to determine its exact age, it is safe to assume that it is younger than 14 or 15 days.

THE EFFECTS OF COLD ON ANIMAL TISSUES.

ROBERT A. LAMBERT, M.D.

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The effect of cold on the animal organism, though full of interest and perhaps of greater practical importance than the effect on individual tissues, will be left for discussion at some future time. While closely related, the two questions should not be confused. Principles governing the effect of cold on the body do not necessarily apply to the effect on its constituent tissues. It is an interesting, and well recognized fact, that isolated mammalian tissues, or even entire organs, can withstand temperatures far below that fatal to the body as a whole.

In considering the effect of low temperature on animal tissues, the first question which arises is: Is the injury due to the low temperature itself or to the associated freezing? This question had been definitely settled in regard to many plant cells

and protozoa through the process of "over-cooling," a well understood physical phenomenon in which the temperature is lowered just under the freezing point without allowing freezing to take place. Such experiments with a number of plant cells have shown that the injury is, for the most part at least, to be attributed to the freezing. We have applied practically the same principle to studies with animal cells—tissues of the chick embryo—with the following technique: Hanging-drop culture preparations, composed of small bits of tissue in coagulated plasma, were placed for forty-eight to seventy-two hours in an ice box at -7° to -8° C. a temperature around the freezing point of chick tissue. When removed from the ice box some of the preparations were found to be frozen, while others were not, a result to be attributed no doubt to accidental variations in the salt content of the drops of plasma due to evaporation. The number of frozen or unfrozen preparations can be more definitely controlled by purposeful variations in the salt content of the plasma, a procedure which experience has shown is not of itself in any way harmful. Such frozen cultures do not show upon subsequent incubation any growth phenomena whatsoever, while the unfrozen cultures grow practically as well as the controls which have not been exposed to cold at all. This experiment demonstrates then a striking contrast in the effects on animal tissue produced by freezing and by subjection to a temperature around the freezing point at which the tissue remains unfrozen. The experiment, however, does not settle the question as to whether *prolonged* exposure to a temperature just above the freezing point may not be in some degree harmful.

The results of another series of studies throws some light on this point. A comparison was made of the duration of life of embryonic chick tissue kept in hanging drop cultures at room temperature ($+15$ to 18° C) and at a temperature a little above the freezing point (-4° to -6° C). At the end of different periods (two, three, four, five, six, seven, eight, ten and fifteen days) the pieces of tissue were transferred to fresh drops of plasma and placed in the incubator at 37° . Two-, three-, four- and five-

day preparations in both series gave good growths. Preparations kept for longer periods in the ice box showed proportionately lessened growth, and after ten days exposure were always negative. On the other hand, those kept at room temperature for ten days were uniformly positive, and growths were occasionally obtained from fifteen-day preparations.

These experiments show then that embryonic tissue may be kept alive longer at room temperature than at a temperature just above the freezing point of the tissue. This lessened vitality at the lower temperature may perhaps be interpreted as the result of some derangement in the metabolism in the cell leading to an accumulation of injurious products. An instance of disturbed metabolism due to the effects of cold, one that has received careful study, is seen in the sweetening of potatoes in winter. The cold does not inhibit the activity of the diastase normally present, whereas oxidative processes are greatly retarded, with the result that sugar accumulates (Müller-Thurgau).

It has been observed clinically that limbs exposed to cold for any considerable period, though not frozen, may yet suffer the serious injury known as "frost gangrene." The question as to whether this is a result of a direct cell injury or of an indirect injury through circulatory disturbances, was a subject of much discussion among early workers. Later investigations have shown, however, that this gangrene is due to ischaemia. It was urged by Cohnheim and others that the ill effects of freezing upon the body tissues are likewise primarily due to circulatory disturbances in the part frozen, but it is now agreed that the process of freezing injures the cell directly.

The injurious action of cold on animal tissues is then of two kinds, one direct and toxic in character, the other nutritional.

In the process of freezing how is the injury to the cell brought about? The mechanism of cell freezing will be made clearer by a consideration of the freezing of a salt solution, and of some colloid such as gelatin. Ice forms in salt solution from the water present leaving the salt in concentrated form between the crystals. Gelatin, upon freezing, is left in firm layers between

the particles of ice. The process of freezing of plant cells and protozoa has been directly observed under the microscope. Ice crystals are formed as in salt solutions and in gelatin from the water present. If the cells are quite large (amoebae, phycomyces) the crystals form inside as well as outside the cells. In small cells the crystallization is always extra-cellular. In either case there occurs a marked distortion of the cell body.

The injurious effects of freezing upon cells may be explained in several ways: (1) Through mechanical tearing as the ice crystals are formed. (2) Through the concentration of salt around the crystals. (3) Through the withdrawal of water in the process of ice formation. In regard to plant cells the evidence is strong in support of the view that the withdrawal of water is the chief factor. The experiments supporting this explanation can not be detailed at this time. A certain parallelism has been found to exist between the phenomena of resistance to freezing and to drying by lower forms of life. It has been maintained that in both instances the essential factor is the withdrawal of water from the cell.

Does the injury to the cell or tissue from freezing take place in the freezing or in the thawing? And does the rapidity of thawing influence the degree of injury? Both of these questions have interested botanists. The first presented a difficulty in the matter of separating the effects of freezing from those of thawing. Goeppert, however, using two flowering plants, orchid and begonia, which in death undergo a change in color, was able to show that death took place while the cells were in the frozen state. Similar studies by Molisch with several fluorescent algae added further support to Goeppert's conclusion that the injury produced by freezing is associated with the process of crystallization. Goeppert maintained that it necessarily followed from his work that the rapidity of the thawing was a matter of indifference, but other investigators felt that on account of the limited application of such tests the question as to the possible influence of rapid or slow thawing could not be considered superfluous. In order to settle this point Molisch and Müller-Thurgau,

working independently, carried out experiments in which several hundred plants and certain fruits were used, comparing the results after slow and after rapid thawing. They found that with only three exceptions, all fruits (apple, pear and guava) the rate of thawing did not modify in any way the effect produced by freezing.

What is the effect of subjecting tissues to temperatures below the freezing point? It would seem at first from the preceding analysis of the injurious action of freezing that after a tissue is completely frozen a still lower temperature could produce no further injury. But this has not been found to be the case. It has been shown furthermore that the *duration* of exposure to cold is an important factor. The results of our experiments bearing on these two points—depth of temperature and duration of exposure—are as follows: Pieces of chick embryo heart survive freezing at -10°C from two to six hours but are killed by exposure for twelve or more hours. The same tissue resists a temperature of -20° for five minutes but not for twenty minutes. Lower temperature obtained with a carbon dioxide freezing apparently produces a fatal injury in less than a minute. Rischpler's studies upon the effects of freezing animal tissues *in situ* (rabbits' ears) support the general law, exemplified in the above experiments, that the effect of low temperatures is directly proportional to the depth of the temperature and to the duration of exposure.

The question as to why this should be so has not been satisfactorily answered although several hypotheses have been offered: (1) That certain elements of the cell (e. g. lipoids) are frozen at lower temperatures than the water present. (2) That the crystallization of water, and the consequent drying of the cell, becomes more complete with a longer exposure and a lower temperature. (3) That serious chemical disturbances are produced by very low degrees of cold. (4) That low temperatures affect differently the various metabolic processes in cells, thus causing an accumulation of toxic products. None of these hypotheses is altogether adequate.

The varying resistance to cold of different mamalian tissues has received considerable attention. The ears of guinea pigs and rabbits and the tails of rats and mice are well adapted to such studies. The abdominal viscera, while offering some difficulties for carrying out experiments of this nature, have likewise been subjected to experimental study. Ice-salt mixtures and ether spray have been chiefly employed to induce cold. Morphological studies have shown that if the part be completely frozen all tissues (epithelium, connective tissue, muscle, bone, cartilage, etc.) give evidence of being at least temporarily injured. Shrunken nuclei and vacuoles in the cytoplasm are regularly seen. Prolonged freezing or subjection to very low temperatures causes necrosis. Short freezing repeated at intervals produces, especially in epidermis, a remarkable hyperplastic growth. Atypical division figures and large multinucleated giant cells are found in large numbers in tissue so treated. Certain tissues are much more susceptible to cold than others. The secreting cells of the liver and kidney are easily killed; bone is less resistant than cartilage; muscle is more susceptible than connective tissue. It may be stated summarily that to cold as to other injurious agencies, the more highly specialized cells are least resistant. An apparent exception to this rule appears in the work of Richardson (1867) who stated in his report that the freezing of a pigeon's brain produced only temporary irritative phenomena, and that a pigeon whose cerebral cortex had been frozen forty-five times remained perfectly normal. The fact that he employed an ether spray on the skull in his attempts to produce a frozen condition renders it highly improbable that the brain was frozen at all.

In our tissue cultivation studies the only thorough comparative observations made were with heart muscle and connective tissue of the chick embryo. The latter proved the more resistant but the difference was not as striking as might have been expected. Pieces of heart would occasionally resume beating, upon incubation, after having been frozen three or four hours at

-10° , while six to twelve hours represented, as a rule, the limit for connective tissue.

The great resistance of cancer cells to freezing and low temperatures is well known. Ehrlich found, for example, that a mouse carcinoma frozen for two years at -10° to -14° was still transplantable. Gaylord made comparative studies of the resistance to an extremely low temperature of cancer cells and embryonic cells, inoculating the tissue after exposure as a test of survival. He found that mouse carcinoma cells survived the temperature of liquid air (-180°) for eighty minutes, while the tissues of the mouse embryo were killed by twenty minutes exposure.

We have made similar comparative studies. Instead of transplanting the treated tissue, however, the method of tissue cultivation has been used as a test of survival. The results have confirmed the work of Gaylord as to the greater resistance of malignant tumor cells as compared with embryonic cells. We have also made comparisons between sarcoma cells and connective tissue cells of adult rats. Cultures from both embryonic and adult tissues frozen five minutes at -16° were regularly negative while tumor tissue treated in the same way gave uniformly positive cultures, although growth was less active than with untreated tissue. That embryonic tissue of the chick is much more resistant to cold than mouse embryo tissue is also shown by these experiments.

The last point to be discussed is the effect of interrupted freezing, that is of repeated freezing and thawing, as compared with that of continuous freezing. It has been currently accepted that a fatal cell injury may be produced more rapidly and with greater certainty by interrupted freezing than by continuous freezing. Theoretically there is some basis for this belief inasmuch as the factor of mechanical tearing would apparently be increased. It has been shown too that red blood corpuscles of several species are not readily destroyed by freezing once but are easily broken up by repeated freezings. Rigid experimental proof of this principle as regards other animal tissue cells, is,

however, difficult to find.* On the contrary, considerable work has been done which indicates that the duration of exposure and the depth of the temperature are much more important factors. Fuerst, for example, found that freezing a rabbit's ear eight times with intervals of fifteen or thirty minutes between the freezings does not cause any marked destruction of tissue, whereas it has been shown by Rischpler and others that ten to thirty minutes continuous freezing is followed by wide-spread necrosis and sloughing.

Summary.

1. Low temperatures associated with freezing produce a direct cell injury. The injury is probably produced through the withdrawal of water in the process of crystallization.

2. Temperatures slightly above the freezing point, are harmful if long continued. In extremities the result is gangrene from circulatory disturbances. With cultures of chick tissue the effect is probably due to a derangement of cell metabolism.

3. The influence of the rate of thawing is negligible.

4. The effect of extremely low temperatures is proportional to the duration of exposure and depth of temperature.

5. Body cells vary in their resistance to cold. The highly specialized organ cells show least resistance. Cancer cells are more resistant than the cells of normal adult and embryonic tissues.

6. Repeated freezing of an extremity produces less harm than a single long continued freezing. Short freezing at intervals induces in certain tissues a remarkable hyperplastic growth. Long continued freezing is followed by complete necrosis and sloughing.

*Recent experiments with pieces of chick embryo intestine have shown that while a few cells grow out in cultures after rapid freezing and thawing three times, a more diffuse growth takes place from tissue frozen continuously at the same temperature (-16°C) for the same length of time; that is, a somewhat greater injury is produced by interrupted freezing.

Discussion.

DR. STEWART: It is very surprising how many contradictory reports one finds in the literature regarding freezing. I have read numerous papers that have been written regarding the effect on life of freezing. One man will say emphatically that the frog can be frozen stiff and another will say just as positively that it cannot.

Referring to the difference between the resistance of cancer cells and embryonic cells this seems very important, because it was the tendency before Dr. Lambert's paper to regard the destructive effect of freezing as a purely mechanical process. His work, however, shows that the mechanical theory does not explain all. Here is a cancer cell which is frozen just as hard and an embryonic cell, and yet the one lives and the other does not. There certainly must be a more deep seated process than the mechanical process.

DR. LAMBERT: The cells of the transplantable rat and mouse tumors show a far greater resistance to cold than either the normal or embryonic tissues of these species. Embryonic chick tissues, as I stated before, are more resistant than those of rats and mice.

I emphasized the point as to the difference in the effects produced by interrupted and by continuous freezing because it is a current belief that the former produces the greater injury, an opinion so far as I have been able to ascertain, not based on experimental work.

The reader whose interest leads him further into this subject will find in the two following treatises references to the literature:

¹MOLISCH: *Untersuchungen über das Erfrieren der Pflanzen*, Jena, 1891.

²MARCHAND: *Die Kälte als Krankheitsursache*; Krehl u. Marchand, *Handbuch der Allg. Path.*, Bd. 1, Leipzig, 1908.

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DR. W. G. MACCALLUM, *President.*

HYPOPLASIA OF THE KIDNEYS.

F. R. MOUNT, M.D.

The organs here presented were taken from a foundling baby, admitted to the New York Nursery and Child's Hospital, March 26, 1912, aged 14 days, on the service of Dr. Kerley, to whom I are indebted for the report of the clinical history. It was in poor physical condition on admission, and during its stay of ten days gradually lost, dying apparently of inanition; weight shortly before death was 4 lbs. 5 ozs. There was no record of urination, but it is improbable that dry diapers would have passed without notice.

Autopsy was performed April 5th, 24 hours post mortem. Male child, white, poorly nourished, 46 cm. in length. Feet in at-

titude of moderate equinovarus, more marked on the right side; no other deformities apparent. Aside from the urogenital organs, there were no important changes in the viscera. The kidneys did not present the usual retroperitoneal prominences alongside the vertebral column, but their positions could be identified by the distinct course of the ureters. Adrenals, kidneys, ureters, and bladder were removed together. The adrenals appear of normal size, color, and consistence; section shows the usual midzone hyperemia.

The right kidney is slightly smaller than the left, each being smaller than its corresponding adrenal; the contrast is exaggerated, due to the depth of the concavities on the under surfaces of the adrenals which the kidneys occupy. The surface of the right kidney except for indistinct lobulation is smooth; on section the cortex is 1 mm. thick, the medulla 3-4 mm. The hilus is completely filled with dense tissue occupying the usual position of the pelvis. The lumen of the ureter appears to end blindly in a slight enlargement; the apices of the papillæ are thus separated from the ureteral cavity by a wall of tissue varying from 1 to 3 mm. in thickness. The surface of the left kidney has scattered nodular prominences, slightly paler than the surrounding kidney tissue, from 1 to 3 mm. in diameter. Some are solid, others distinct thin-walled cysts. On section the cortex is about 1 mm. thick: pyramids are of very unequal size and shape, the outlines being partly obscured by the presence of fairly well-defined yellowish white nodules. Vessels are injected, but the markings are extremely irregular. There is a large amount of tissue in the region of the hilus, as in the right kidney. The ureters were not probed before fixation. In the lower portion they appear of normal caliber but the wall seems thick and nodular. Nearer the kidneys the lumen is distinctly narrowed. The bladder is contracted, and contains a small amount of clear urine; there was, therefore, some secretion by the kidneys. In tracing the vas deferens, no seminal vesicle could be found on either side.

Histological examination revealed nothing abnormal in the lungs, liver, heart, spleen or intestines. Pancreas showed slight

intra- and perilobular cirrhosis. Adrenals showed the customary degeneration of the inner cortical zone with hyperemia.

Right kidney with low power is easily separated into an outer spongy zone and the more solid medulla. In the cortex the tubules are lined with swollen granular ragged epithelium, resembling normal convoluted tubules; the cells however are granular, and in some places filled with large "colloid" droplets. The lumen frequently contains granular material. Between these are greatly dilated tubules or cysts whose walls are lined by a single layer of more or less flattened cuboidal epithelium. In addition there are scattered small tubules resembling the Henle loops. The glomeruli are mostly well-formed, but in the superficial portion, occasional rudimentary glomeruli of small size and with the tuft covered by cuboidal epithelium may be found. In the medulla the tubules are extremely irregular in shape and caliber. They are lined by cylindrical epithelium of the usual type with distinct cuticular border. In some of the pyramids, the tubules are widely separated by a very cellular connective tissue of loose texture; scattered through this are occasional groups of round cells, and eosinophiles; some of the former are undergoing mitosis, the appearance suggesting active blood formation. The left kidney presents a similar, though somewhat more complicated structure. Distinction between cortex and medulla is not clear cut. The capsule is thickened and contains smooth muscle fibers; in several sections are small tumor like masses, lying partly within the capsule and composed of polygonal cells filled with fat globules of varying size, which are not anisotropic and stain bright red with Scharlach R. These are evidently small lipomatous tumors and not aberrant adrenals. The cortex shows a structure resembling that of the other kidney. The cyst-like spaces reach a large size. They frequently show heaping up of cells at some portion of the lining, or a spur formation resembling incomplete septa. The medulla also resembles that of the other kidney. Some of the pyramids appear to contain more numerous tubules than others; where the tubules are few, they show marked dilatation.

Scattered through both kidneys, but more numerous in the

left, are islands of embryonic cartilage. They lie immediately beneath the capsule, also along the large vessels entering the hilus, and in various parts of the cortex. They are surrounded by concentric layers of connective tissue cells, and are quite sharply demarcated from the surrounding kidney tissue.

Sections through the left ureter shows a pelvic branching into two short arms. As has been said there is no dilatation into a true pelvic cavity, and the end is surrounded by a thick mass of tissue composed of smooth muscle fibers and connective tissue which appears to separate it from the kidney tissue proper. Failure of the collecting tubules to unite with the pelvis immediately suggests itself as a possible explanation for the malformation of the renal tissue. In some sections, a direct connection can be demonstrated between the collecting tubules and the rudimentary pelvic cavity; but many of the papillae seem to be closed at the apices by a circumferentially disposed stratum of fibrous tissue, and it is the tubules in these papillae which apparently show the greatest distention. The cavity of the rudimentary pelvis and its continuation into the ureteral lumen is lined by squamous epithelium of normal type but varying greatly in thickness in different regions; in some places there is a localized heaping up of cells.

Blood vessels show no especial change; there is a rich capillary supply to the young connective tissue which constitutes the bulk of the pyramids.

The literature contains reference to a number of cases similar to this. Aschoff¹ refers to the condition in his text as "Hypoplastische Zystenniere," and cases have been reported by v. Mutach,⁴ Rückert,⁶ Busse,² Meyer,³ Natanson⁵ and others.

The kidneys are considerably smaller than the normal.

	<i>Right</i>	<i>Left</i>
Measurements (after hardening) . . .	20x7x5 mm.	25x10x10 mm.
Average measurements (Vierordt) 50x24x17 "		49x25x17 "
Weights (after hardening)	0.65 gms.	1.70 gms.
Average weights (Vierordt)	10.5	

Cartilage is not uncommon in the teratomatous tumors of the kidney, but in the reported cases these are large tumors show-

ing rapid and malignant growth with tendency to metastasize. Aside from the cartilage there is nothing in this case to justify a belief in the teratomatous nature of these kidneys, especially since the histological elements and characteristically the striated muscle fibers, of renal mixed tumors are wanting. The presence of the cartilage, on the other hand, is hard to explain. Of the possible sources, first the inclusion of aberrant skeletal tissue, and secondly a metaplasia of the young connective tissue, the latter seems more probable; but there is no real basis for decision.

In regard to the cystic structures, Virchow's original idea that the cysts were sequellæ of inflammatory conditions of the papilla, or obstruction by uric acid deposits has been generally abandoned. Evidence of inflammation in the papillæ is not found and the frequent association of other developmental anomalies, as absence of the seminal vesicles in this case, points to congenital rather than acquired causation. Of the theories which explain cysts as neoplasms and those which attribute the cysts to a failure of union of the component parts of the urinary system, the latter appears more plausible, and is more generally held. The study of this case has led to the tentative conclusion that there has been a defective connection between uriniferous tubule and ureter; the exact situation of the defect, whether down in the papillæ as would seem evident from some portions and in contradiction to the current conception, or where the collecting tubule begins we have as yet been unable to decide.

A more complete description will be published later.

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Discussion.

DR. F. C. WOOD said that he could not add anything new to the discussion of this case as he had never seen a specimen of exactly this type. He was under the impression that in the ordinary congenital cystic kidney the whole tissue was much more spongy than was shown in this specimen. The fact that the cystic change was not very extensive would give a wonderful opportunity to Dr. Mount to ascertain the exact site of the obstruction.

DR. MACCALLUM: There are several well-known types of congenital cystic kidney. In those of which Dr. Wood spoke one can make out relatively little because of the great distortions. Others found at birth show somewhat simplified conditions. I had at one time a reconstruction made by Dr. F. M. Meader of a cystic kidney found in a newborn infant which was otherwise much malformed, with cysts of the liver and supernumerary digits. In this instance the kidneys were large, soft and gelatinous, containing small cysts and were of such size that they had to be removed before the child could be delivered. It seemed possible to make out cysts connected with glomeruli and others connected with the conducting tubules.

Since that time I have seen a number of examples of another type of which fusiform cysts were found in the pyramids without any evidence of obstruction at any point. This condition is sometimes seen in the adult.

Of course the most plausible idea of the origin of the cystic kidney is that the two portions of the tubules which ordinarily unite are prevented from doing so. In Dr. Mount's case, however, there seems to be a different point of obstruction, namely between the ureteral anlage and that of the tubules.

DR. MOUNT: The appearance of the kidney was as if the ureter had stopped at the pelvis and had not given off secondary branches to unite with the collecting tubules.

ADRENAL HEMORRHAGE IN A CHILD.

A. M. PAPPENHEIMER, M.D.

The subject of this report was a previously healthy, handsome, well-nourished boy of three years, who was born and lived at the Nursery and Child's Hospital. I am indebted to Dr. Freeman for the clinical history, and to Dr. Sawyer, the House Physician, for additional notes.

On the evening of April 29th, the child had gone to bed, apparently in perfect health. At 2:30 in the morning the house physician was called, and found him vomiting, irritable and delirious, with a temperature of 103°. In the morning he was again summoned because the child was having convulsions. A mustard bath was given, after which the child lay in an apathetic, semi-conscious state until its death at 12 o'clock, nine and a half hours after the onset of the symptoms. It was slightly cyanosed; the respiration became slow and gasping; the pulse was somewhat rapid, but fairly strong until a short time before death, when it failed to respond to injections of ether and camphor.

The autopsy was made the following morning. The body was that of a large, very well-nourished child, of neither pasty nor obese habitus. There were a few scattered purplish petechial spots over the trunk and extremities, and more numerous small bright red hemorrhagic blotches in the visceral and parietal peritoneum. Eyes, ears, nose and teeth were normal. The thymus was large, fleshy and lobulated, and weighed 19 gms. The heart seemed relatively large, and there was a distinct hypertrophy of the left ventricle. On the aortic surface of the anterior mitral leaflet were a few atheromatous patches, and the aorta above the sinuses seemed slightly thickened. There were no other cardiac lesions or anomalies. The lungs, aside from moderate congestion and œdema, were normal. The liver was rather opaque and friable, but otherwise unchanged. The spleen was slightly enlarged, firm, dark and smooth on section. The follicles were very numerous, of moderate size, not prominent above the surface.

There was an excessive lymphoid hyperplasia throughout.

Tonsils and lingual follicles were large. In the small gut, the solitary follicles and the Peyer's plaques were exceedingly conspicuous as was the lymphoid tissue of the appendix. Aside from slight hyperæmia of some of the Peyer's plaques, and for the presence of scattered punctate hemorrhages in the mucosa of the stomach and small intestine, the alimentary tract was normal throughout. The intestinal contents consisted of loose yellow fecal matter with a slight admixture of mucus. The mesenteric lymph-nodes were extremely large, up to 2 cm. in length. Most of the glands were pale and firm, a few showed central areas of hemorrhagic softening. The kidneys were pale, with injected blood vessels. The brain was large, dry and congested. The ears contained no exudate. The lesions of chief interest were those found in the adrenals. The cellular tissue about the glands was noticeably œdematous. The adrenals themselves were of normal size and shape, but on section, both glands showed a diffuse hemorrhagic infiltration, and were of a uniform dark red color. The demarcation between cortex and medulla was, however, still obvious in certain portions. There had been no extravasation into the surrounding cellular tissue.

The microscopic sections show that the diffuse hemorrhage into both glands has led to a complete destruction of the medullæ. Only a few scattered chromaffin cells are found, and for the most part, the medullary area is occupied by a closely-packed blood mass in which no other cellular elements are present. The architecture of the cortex is better preserved. The capillary walls are in places still recognizable. Between the capillaries and surrounded by red-cells, lie the cortical elements. Many of the cells still have a well-stained nucleus and a fringe of vacuolated cytoplasm. Others show pycnosis and even fragmentation of the nucleus. The columnar alignment of the cells in a few places, beneath the capsule and about the central vein, is still preserved.

The capillaries are most often collapsed; their wall seems somewhat thickened, but the nuclei of the endothelial cells are not swollen. In some of the capillaries are small groups of polynuclear leucocytes, in others hyaline thrombi. Some of the larger

veins contain platelet thrombi, which for the most part do not obstruct the lumen completely.

The hemorrhage is practically limited to the glands, but in one block, there is found a small rupture through the capsule into the adjacent tissue.

It is interesting that the extra-cortical adenomata, several of which were found in the sections examined, are entirely free from hemorrhage. They are of considerable size, and their presence in an uninjured condition might perhaps justify one in the inference that an insufficiency of cortical tissue was not the cause of death.

The nerves and sympathetic ganglia about the glands appear normal. There is an abundant exudation of fibrin forming a more or less continuous sheet about the glands.

The histological study of the remaining organs showed some features which deserve mention. The centers of the lymphoid follicles in the spleen, intestines and certain lymph-glands are composed of large phagocytic cells filled with chromatin fragments, apparently derived from fragmented, pycnotic lymphoid cells. The lesion resembles that described by Flexner in his study of lympho-clytoxins, and is a familiar one. In the liver, however, an interesting observation was made. The liver capillaries contain numerous, dark staining bodies, varying in size from that of a liver-cell nucleus to small coccus-like particles. These are undoubtedly free nuclear structures in various stages of degeneration. The larger bodies are crescentic in shape; the chromatin is condensed against the nuclear membrane, the central portion being pale. How is the presence of these degenerating nuclear particles to be explained? Obviously, they are not derived from the liver elements themselves, since the hepatic cells and the capillary endothelium show no degenerative changes. Possibly they are derived from the fragmented and pycnotic nuclei which are found in the lymphoid follicles of the intestine and mesenteric glands, and which have been swept into the liver.

In the myocardium, there were found, scattered through the musculature, small collections of polynuclear leucocytes. A dis-

ting necrosis of the muscle fibers in these areas could not be made out.

The kidneys show an intense degeneration of the cells of the convoluted tubules. Some of the cells appear to have undergone actual necrosis; all of them are granular, swollen and stain intensely with eosin.

The cause of this fulminating illness is obscure and mysterious. Cultures made from the spleen on plain and serum agar remained sterile after four days, and we have no basis for grouping the case with any of the known infections.

The numerous cases of adrenal hemorrhage which have been reported fall into several groups. One of these groups includes the large number of cases observed in still-born or new-born infants, in which birth-trauma or manipulations to start respirations may be regarded as initiating the hemorrhage. The great fragility and hyperemia of the inner cortical zone, which begins its regressive changes at this period, may be looked upon as contributory. In other cases of this group, the adrenal hemorrhage may be part of a general hemorrhagic infection or diathesis. Cases of this sort have been presented to the Society at various times by Prudden, Hodenpyl and Norris.

The cases occurring in adult life have been frequently associated with thrombosis of the adrenal veins, or of the inferior vena cava; trauma during abdominal operations is also an occasional cause. In still other cases of so called adrenal apoplexy, no definite cause can be discovered. Large blood cysts forming palable tumors, may be formed, and since the lesion is not always bilateral, recovery after operation is possible.

There is, however, a group of cases, closely resembling the one here reported in their clinical course and pathology, in which without previous history of infection or other illness, a child suddenly becomes extremely ill, with high temperature, vomiting, diarrhoea, prostration and convulsions, and dies within one or two days. Often a purpuric rash of greater or lesser intensity develops. Cases of this sort have been reported by Batten,¹ Andrews,² Voelker,³ Langmead,⁴ Waterhouse⁵ and others. The autopsy re-

veals a diffuse hemorrhage into both adrenals, with scattered hemorrhages elsewhere. Cultures from the blood, spleen and from the adrenals themselves, when these have been made, have usually been sterile, although Riesman has reported several cases in which staphylococci were recovered post-mortem, and other pyogenic bacteria have occasionally been found. In the majority of cases, the etiology is obscure. The fact that similar lesions may be produced in animals by the injection of diphtheria-toxin and other poisons of bacterial origin, suggests the possibility that these cases, in spite of their striking clinical and pathological similarity, are not necessarily all due to the same toxic or infectious agent.

In reviewing the history of these cases, moreover, it is not easy to know which symptoms are attributable to the hypothetical intoxication or infection, which we must assume to be the cause of the adrenal hemorrhage, and which to the destruction of the adrenals. We know from animal experiments, that double extirpation is regularly followed by death, the fatal outcome being delayed only in those animals such as rats, in which there is an abundance of accessory adrenal tissue. The animals die with symptoms of extreme asthenia, motor weakness and subnormal temperature. There can be no doubt that an extensive destruction of the adrenals, as in the case here described, is amply sufficient to cause death. Materna,⁶ however, has suggested that the symptoms produced are rather those of an acute adrenalian intoxication, than an acute insufficiency, believing that with the hemorrhage, a toxic amount of adrenalin, or of the physiological equivalent, is swept into the circulation. With the blood serum from a fatal case, he obtained a positive Vulpian reaction and a positive frog's eye test. Although we no longer consider these tests as altogether specific, some support for this idea is found in the clinical history of initial delirium, excitement, vomiting and convulsions, symptoms which are produced in animals by the subcutaneous injection of toxic doses of adrenalin. The preservation of a strong pulse until just before death also suggests the presence of a pressor substance in the blood.

What role the sudden destruction of the cortex plays in the

production of the symptoms, is, of course, entirely problematical. The presence of a considerable amount of uninjured cortical tissue in the form of extra-capsular, adenomatous masses, did not in this case, suffice to ward off the fatal outcome.

It would seem that a careful study of these cases, clinically and bacteriologically, would be of great interest. Because of the uniformity in the clinical and pathological findings, it does not seem improbable that we are dealing with a specific disease of unknown origin. Moreover a careful examination with modern clinical and laboratory methods, might throw light on some of the many problems of adrenal physiology.

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Discussion.

DR. C. FIELD: Dr. Pappenheimer's case is very interesting. Adrenals exactly similar to these of Dr. Pappenheimer's are seen not only in children as a result of diphtheria, but are a constant finding in animals dying from a lethal dose of diphtheria toxin. I have also come across similar lesions in ricin poisoning. In one case a kid injected with a large amount of diphtheria toxin and killed four hours later by bleeding, showed a tremendous hemorrhagic condition of the right adrenal, the toxin being injected in the right hind leg, the right adrenal being three times as large as the left. An especially interesting point in Dr. Pappenheimer's case is that he found small hemorrhages in the stomach and intestines, which is also a fairly constant condition in death from diphtheria toxin and ricin toxin.

DR. MACCALLUM: Two possibilities suggest themselves in this case. I have asked Dr. Pappenheimer whether the child may have had diphtheria, because such hemorrhages occur in the

course of diphtheria. The other etiological factor which we saw illustrated in a recent case is the mechanical injury to the adrenals. In that instance, a woman who had been operated on for an umbilical hernia showed an extensive hemorrhage in the medulla of the adrenal.

CARCINOMATOUS CYST OF PANCREAS.

J. GARDNER HOPKINS, M.D.

The specimen presented was obtained at autopsy on the body of a man aged seventy-six years. His past history was negative. Up to five weeks before death he had been apparently in good health, but at that time his family noticed that he was becoming jaundiced. He had for some time before this been very slowly losing weight, but about this time the loss of weight became more rapid, although its extent was unknown. On admission to the hospital, three weeks later, he was intensely jaundiced, quite weak, and apathetic. He complained of an indefinite dragging sensation in the region of the stomach, but presented no other symptoms. On examination he was markedly emaciated, and there was slight tenderness in the right hypochondrium. The examination was otherwise negative. His stools were acholic. His blood showed a moderate anæmia of the secondary type. His asthenia became more marked and a few days before death there was a slight rise of temperature to 100 or 100.5°. Three days before death sugar appeared in the urine for the first time. The clinical diagnosis was carcinoma of the head of the pancreas or of the gall-ducts. At autopsy a large thin-walled cyst, about 7 cm. in diameter was found lying posterior to the descending portion of the duodenum to the right of the head of the pancreas. It was filled with chocolate colored turbid fluid. This contained changed blood and a diastatic ferment.

The cyst wall was about 1 to 2 mm. thick, and the lining was

smooth except at the point where it was attached to the pancreas. Here it was puckered and raised into minute papillæ. Between these was a small opening through which a probe could be passed for some distance into the pancreas, evidently following an accessory duct. The tissue at this point was quite firm, but there was no appreciable tumor mass. The pancreas itself was almost completely replaced by fat. The duct of Wirsung was dilated throughout its extent to a diameter of about 3 mm., and immediately surrounding it were some grayish patches of pancreatic tissue. The peripheral portions of the gland were entirely replaced by yellow fat in which were some areas of fat necrosis. Although the duct was dilated, as if from obstruction, a probe could be readily passed through the papillæ into the duodenum. The common bile duct was enormously dilated to a diameter of 2 cm., as was also the cystic duct. The walls were thin and of a deep green color. After the organs had been removed a probe was passed readily from the common duct into the duodenum so that the obstruction was due apparently to pressure of the cyst, which lay directly behind the papilla. The liver was deep olive green and on section small drops of pus exuded from dilated bile ducts in various portions of the organ. The other organs showed little of note. There was a small area of bronchopneumonia which may have been the immediate cause of death.

On section through the cyst wall where it was attached to the pancreas, the lining consisted of from two to six layers of flattened epithelial cells with small deeply staining nuclei. Immediately adjacent to this was a mass of dense fibrous tissue, poor in nuclei, in which there were no remnants of pancreatic acini but numerous islands of Langerhans. Some of these showed areas of mucoid degeneration, but the remaining cells stained well and appeared normal. Scattered through the fibrous tissue were small groups of epithelial cells, rarely more than six to eight in a group. Many of these cells were large and contained very large nuclei, consisting of a ring of densely staining chromatin with one or two nucleoli in the center. These cells were seen to live in the sclerotic walls of some of the vessels. Sections through the body of the pancreas showed a very few remaining

acini of glandular cells which showed little evidence of post-mortem digestion. No islands of Langerhans were found in this portion of the gland. The epithelium of the dilated duct of Wirsung was in places thrown up in papillæ, in other places completely desquamated. In sections of the liver the cells about the smaller bile ducts were crowded with yellow pigment. About the larger ducts there were wide areas of necrosis and in the necrotic areas there were masses of pus cells.

The case must be considered either as a carcinoma developing in the wall of a benign pancreatic cyst, or as due to compression of the ducts by a malignant growth. The neoplasm was so very small in extent that it seemed probable that it was secondary to the cyst formation. The biliary and pancreatic obstructions were apparently due not to the neoplasm but to compression of the ducts by the cyst.

Discussion.

DR. EWING: A moment's glance at the sections in this case inclines one to believe that the process is a carcinoma.

THE RELATION OF EXPERIMENTAL ANÆMIA TO PERNICIOUS ANÆMIA.

E. E. BUTTERFIELD, M.D.

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I think most of us are agreed on one point at least in experimental medicine, that is, that the results of animal experimentation are at the best only an approximation of the conditions encountered in human pathology. It is, therefore, safe to state in the beginning that an experimental pernicious anæmia corresponding in symptoms, course, and pathological anatomy to progressive pernicious anæmia of human pathology is as yet far from

realization. What, then, has been the utilizable yield of the large amount of experimental work on anæmia, which has accumulated within the last 30 years? Let us take up this work briefly in its relation to some of the problems of pernicious anæmia.

As early as 1890 it was known that erythroblasts were to be found in the spleen of guinea-pigs and cats after bleeding. Shortly afterward the same observation was made in the toxic anæmias. The significance of these observations was first brought home to clinicians and pathologists when descriptions of myeloid tissue in the spleen and liver of man in severe anæmias began to appear in the literature. Numerous valuable contributions along this line in human pathology appeared from 1900 on. The most comprehensive was that of Meyer and Heineke,¹ in which the great similarity between the mode of hæmatogenesis as well as between the types of blood-cells in the fœtus and in pernicious anæmia was duly emphasized. An additional analogy was established, the existence of a high color-index in fœtal blood.³ At the suggestion of Meyer and Heineke, Morris³ and v. Domarus⁴ studied the anæmia produced in rabbits by phenylhydrazin derivatives and obtained severe anæmias of long duration, which had many features in common with human pernicious anæmia. These features were foci of myeloid tissue in the spleen and liver, normoblasts, red corpuscles with granular basophilia, and occasional myelocytes in the circulating blood. These phenomena were interpreted simply as evidence of blood-regeneration. Morawitz and Blumenthal,⁵ Itami,⁶ and Ritz⁷ objected to this interpretation on the ground that they found essential differences between the toxic and post-hæmorrhagic anæmias. According to them the animals with toxic anæmia regenerated more rapidly and developed more constantly extramedullary foci of myeloid tissue. Itami believed that the extramedullary myeloid tissue was not a manifestation of simple regeneration, but developed in response to some more definite chemical stimulus. In a parallel series of experiments on post-hæmorrhagic anæmia, in which one set of animals received injections of laked blood he found more active regeneration in that set and came to the conclusion that some constituent of the disintegrated red corpuscles furnished the nec-

essary stimulus to regeneration. Serum seemed to be without effect. Itami expressed doubt as to whether myelo- and erythropoiesis in the spleen would ever be produced by repeated blood-letting alone. By alternately bleeding rabbits to the point of severe anæmia and then letting them recover, Skornjakoff⁸ then proved that myeloid foci could be produced constantly in the spleen, less frequently in the liver; normoblasts in large numbers, red corpuscles with granular basophilia, and myelocytes occurred at times in the circulating blood. The only remaining difference then between the post-hæmorrhagic and the toxic anæmias would be in the rapidity and constancy with which these characteristic changes could be produced. Most recently Milne* has shown that even this difference does not exist. Repeated small bleedings in rabbits are followed promptly by the appearance of erythroblasts and red corpuscles with granular basophilia. Dr. Milne has also produced more extensive areas of myeloid tissue in the liver than have been described heretofore in any of the experimental anæmias. This would seem to restore the validity of the interpretation first advanced: a simple regeneration is sufficient to explain the picture found in the blood-forming organs in pernicious anæmia and in the experimental anæmias.

Quite apart in scope and purpose from the work just considered there is another group of experiments on toxic anæmia, which arose from observations on the bothriocephalus anæmia. It will be remembered that after Tallquist⁹ had produced anæmia experimentally with a hæmolytic substance obtained from the proglottids of *Bothriocephalus latus*, Faust and Tallquist¹⁰ succeeded in isolating and identifying the hæmolytic agent as the cholesterin ester of oleic acid. In their feeding experiments they found that this substance was split into cholesterin and oleic acid in the intestine and was resorbed in the chyle as oleic acid or

*Unpublished work, to appear in *Journal of Experimental Medicine*, Vol. 16, p. 325. I am very much indebted to Dr. Milne for the privilege of drawing freely on his unpublished results to-night. This work rounds out fairly completely the picture of protracted post-hæmorrhagic anæmia in rabbits and establishes more clearly than any previous work the analogy between this condition and pernicious anæmia of human pathology.

Na-oleate. The chyle became strongly hæmolytic. The presence of such a high percentage of free acid or soap in the chyle resorption of oleic acid from the intestine is quite out of harmony with the prevalent and apparently well established views on the resorption of fats. This discrepancy has not yet been cleared up. Recently H. M. Adler¹¹ has studied the anæmia produced in rabbits by olive oil and oleic acid and embodied his results in a paper entitled "experimental pernicious anæmia." According to the descriptions, however, neither the blood picture, nor the course, nor the pathological anatomy resembles pernicious anæmia any more or even as much as do the acute anæmias produced by the phenylhydrazin derivatives. On the whole, therefore, it cannot be said that the experiments with substances isolated from the *Bothriocephalus* have been as successful in imitating the blood-picture and pathological anatomy of pernicious anæmia as has been the experimental work on post-hæmorrhagic anæmia.

I have purposely made no reference to a high color-index in the experimental anæmias, for, it seems to me that proof is lacking that this almost pathognomonic symptom of pernicious anæmia has been successfully imitated in the experimental anæmias. On looking over Tallquist's figures one finds that his apparently high indices are with one exception due solely to his manner of calculation.

Let us now turn to some more general features of severe anæmias. In 1909 Boggs and Morris¹² called attention to the occurrence of lipæmia in the post-hæmorrhage anæmia of rabbits. This occurred quite constantly and became marked when the red corpuscles fell below 2,000,000. From the milky serum they isolated 2% to 4% of an oily substance which gave very high figures for iodine absorption although it did not reduce osmium tetroxide. In accordance with the work of Cohnstein and Michaelis¹³ the first assumption would be that the organism was unable to oxidize its fat on account of the reduction in the number of red blood corpuscles. It will be recalled that Cohnstein and Michaelis showed that for the disappearance of chyle-fat from the serum, red blood corpuscles or laked blood and oxygen were

necessary. Serum alone was without effect. The explanation is somewhat shaken by the fact that in the toxic anæmias with the same reduction in the number of red blood corpuscles and hæmoglobin lipæmia did not occur (Boggs and Morris). This may constitute an essential difference between the toxic and the post-hæmorrhagic anæmias.

The nitrogen metabolism in anæmia has long been a subject for discussion.¹⁴ It was claimed at first that there was a daily loss of nitrogen following repeated blood-letting. This seemed to be overthrown when Van Noorden¹⁵ found a marked nitrogen retention instead of a deficit in pernicious anæmia. On looking over Van Noorden's cases it will be found that the metabolism was studied during periods of regeneration and it is therefore to be expected that the nitrogen balance would be positive. In a disease of such a remittent course it is necessary to have long series of determinations carried through the periods of blood destruction as well as regeneration. In fact Rosenquest¹⁶ found great irregularity in the nitrogen balance in pernicious anæmia, although a definite relation to the condition of the blood was not apparent. Although metabolism experiments in the experimental anæmias, toxic and post-hæmorrhagic, would go far toward clearing up the apparently contradictory views, trustworthy results have not yet been forthcoming. Some general observations have been made in the post-hæmorrhagic anæmias which may indicate roughly what is going on. In the first week of the anæmia after from 80 to 100 ccm. of blood have been withdrawn there is regularly loss of weight amounting to 300-400 grams, that is $1/6$ to $1/5$ of the initial weight.¹⁷ When the bleedings are pushed further the loss of weight continues and if the animals are killed after a period of protracted sustained anæmia there is an almost complete disappearance of subcutaneous and abdominal fat.¹⁸ Associated with this there is fatty change and hæmosiderosis* of the organs with

*It is difficult to conceive why such marked hæmosiderosis should occur in post-hæmorrhagic anæmia. Morawitz assumed that the newly formed red blood corpuscles were less resistant than the normal ones. Direct determinations, however, have shown that the resistance to hypotonic solutions is not diminished (Milne).

central necrosis in the liver. It is quite evident that there is a profound disturbance of nutrition in a sustained post-hæmorrhagic anæmia. On the other hand, if the animals are allowed to recover the body weight rises and after a period of regeneration may surpass the initial figure. In Skornjakoff's experiments on post-hæmorrhagic anæmia of 5 to 6 months duration with alternating periods of severe anæmia and regeneration the body weight of the animals during the last period of regeneration was about the same as at the commencement of the work. Over a liter of blood was withdrawn in one of these experiments.

In summing up: The one fact which stands out clearly as a result of the work on post-hæmorrhagic anæmia is the almost complete analogy between this condition and pernicious anæmia in the changes in the blood and blood-forming organs. This demonstrates that these changes may be interpreted with reasonable certainty as phenomena of regeneration pure and simple. The prompt appearance of red blood corpuscles with granular basophilia following withdrawal of a few ccm. of blood proves conclusively that this granulation is not a result of cytoplasmic degeneration but is an accompaniment of regeneration. Concerning many other problems intimately connected with pernicious anæmia, for example, the question of autochthonous formation of myeloid tissue in the spleen and liver, the genetic relations between the different types of blood cells, the nitrogen balance in different phases of severe anæmia, and the mechanism by which compensation for the diminution in the oxygen carrying power of the blood is effected, the experimental work has as yet yielded no unequivocal results. In fact the positive knowledge which we possess concerning these questions is still almost exclusively the result of clinical, pathological anatomical, and embryological investigation.

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Discussion.

DR. EWING: The work on experimental anæmia has doubtless been of great service in showing what features of the disease in man may be referable to hæmorrhage and some other forms of blood destruction and it has been a pleasure to listen to Dr. Butterfield's able summary of this work. I agree however with Dr. Wood that the true picture of progressive anæmia of man has not been produced experimentally; and I doubt if it can be.

The experimenters have used chiefly blood letting and various hemolytic agents to produce the disease. Yet it is well known that pernicious anæmia in man rarely follows hæmorrhage.

The human being can tolerate many large hæmorrhages and small bleedings frequently repeated over long intervals without developing a progressive fatal anæmia. Likewise there is no adequate evidence to show that any poison is essentially concerned in the genesis of cryptogenic pernicious anæmia. The etiology is quite complex but one important factor which the experimenters overlook is the congenital tissue predisposition which renders certain rather rare human beings susceptible to the disease.

It has never appeared certain that the experimental animals possess this peculiar susceptibility. I have long felt that the essential features of Biermer's anæmia is its progressive fatal tendency and that the tendency depends upon the establishment of an abnormal type of blood production in the bone marrow. The mysterious factor in this change has, I think, not been revealed by the experimental studies.

DR. F. C. WOOD said that Dr. Butterfield's discussion was very interesting. The experimental animal usually chosen was rather unsatisfactory for such work. About 1898 or 1899 he had done some work on the experimental production of so-called pernicious anæmia by the injection of pyrodin, phenyl-hydrazin, etc., using the rabbit, but after a considerable series of experiments had given up the attempt to produce a true pernicious anæmia. Several writers had published statements that by these substances they had produced pernicious anæmia, but Dr. Wood had never been convinced from their reports that the type of anæmia produced was the form which we call pernicious anæmia. It should also be remembered that the true Biermer anæmia is a very different type from the anæmias produced by hemolytic agents in human beings.

DR. BUTTERFIELD: It would seem that different animals regenerate much more rapidly and completely than others. In dogs, for instance, it is quite difficult to produce a severe anæmia, even after repeated withdrawal of large quantities of blood.

As to whether pernicious anæmia is to be interpreted as a manifestation of defective hæmatogenesis or rather as a disease characterized by alternating periods of hæmolysis and regeneration, it seems to me that there is no absolute proof of either view. The strongest argument in favor of the interpretation as a hæmolytic-regenerative process is the fact, that it is possible to imitate roughly in animals the essential pathological anatomical features of pernicious anæmia by chemicals which cause hæmolysis and by repeated blood-letting. The fact that the type of hæmatogenesis in pernicious anæmia differs quantitatively, it is true, but not qualitatively from normal post-fœtal hæmatogenesis and the similarity between the blood-forming organs of the fœtus and the same organs in pernicious anæmia may be and have both been used in support of either view. The occurrence of marked hæmosiderosis in pernicious anæmia points strongly to a primary hæmolysis, especially when correlated with the bothriocephalus anæmia. But it is exactly here that the study of experimental anæmias warns us against drawing hastily the obvious conclusion, for, as already mentioned, intense hæmosiderosis occurs frequently in experimental post-hæmorrhagic anæmia accompanied with regeneration.

PNEUMONIA DUE TO POISONING BY NITROGEN TETROXIDE.

F. C. WOOD, M.D.

When nitric acid acts upon certain metals, such as copper, silver, cadmium, etc., a gas is given off which is composed chiefly of nitrogen dioxide (NO). When this comes into contact with the air it absorbs oxygen with the production of nitrogen tetroxide (NO_2) which is easily visible because of its brownish color. The same reaction as regards the end products occurs when nitric acid acts on organic material. While the inhalation of small quantities of these gases causes no serious discomfort, if the mixture is concentrated or if it is inhaled for a sufficient time, serious and even fatal results occur. Strange to say, however, although there are on record over 250 deaths from the inhalation of these fumes, and many more cases must be unpublished, yet there are only a very few reports of autopsies, and still fewer of the careful microscopical study of the tissues. It may not be without interest, therefore, to show the lesions in the lung of a patient dying of this poison and also the alterations produced in the lungs of dogs by the inhalation of nitrogen tetroxide.

The clinical history of the patient was obscure, but the facts obtained were as follows: He inhaled the fumes from a vessel containing large quantities of nitric acid and what was probably a cadmium silver alloy. The patient felt a sensation of choking and ran to the open air; a few moments later he vomited, and then felt much better, ate a heavy dinner, and was free from symptoms until about six hours after the accident, when he was seized with intense dyspnoea and collapsed. He was taken to the hospital and died seven days after the inhalation. The symptoms were chiefly a most intense dysœna, and pain in the throat and chest; occasionally there was a moderate amount of coughing but this was not a prominent symptom. Physical examination showed an irregular consolidation at the bases of both lungs posteriorly. During his stay in the hospital his temperature ran from 100 to 102; respirations from 44 to 60; pulse from 100 to 140. Me-

themoglobin could not be demonstrated in the blood. At autopsy the chief lesions were a moderately dense lobular pneumonia in the lower and posterior portions of the lungs on both sides and an irregular cavity containing clear fluid and with sharply defined walls in the corpus striatum on each side of the brain. Microscopical examination of the brain lesion showed that the appearance was probably due to an artefact, produced by pressure of the embalming fluid, as the walls of the cavity were perfectly sharp with unaltered nerve cells and fibers up to the edge. The lesion in the lung was most interesting. It assumed the general type of a lobular pneumonia with very marked emphysema between the consolidated areas. The lesion was, however, very irregular in type. The alveoli in some places were filled with blood corpuscles, in others with a fibrinous meshwork, in others with large phagocytic cells containing much blood pigment, in others with masses of desquamated alveolar epithelium, and finally in a few there were plugs of regenerating epithelium. Portions of the lung had completely collapsed and the alveolar walls had undergone considerable thickening so that the lung was carneous. No bacteria could be found by staining.

The picture was so peculiar that a large series of experiments were carried out on animals to determine whether it was possible to imitate this lesion. This was found to be perfectly practicable in dogs. The lesions produced by the inhalation of vapors from a vessel containing nitric acid and copper were extremely severe in animals, and it was somewhat difficult to regulate the dose so as not to cause death within a few minutes from an acute œdema. Those animals which breathed a very dilute mixture or had only a single deep breath of the concentrated gas, survived, and often recovered entirely. For two or three days the animals suffered a good deal of dyspnoea with frequent coughing up of frothy mucus. After four or five days the animals usually improved, though some remained feeble and sick for some time longer. Microscopical examination of the lungs at different stages showed after twenty-four hours an acute exudative inflammation with much blood and serum. Later the alveolar epithelium began to regenerate; the ends of the finer bronchi were often plugged with connective tissue or

cells, the appearance which has been called by Fraenkel "bronchiolitis obliterans."

In every way, then, the animal lesions were practically identical with those seen in man, if we allow for the slightly different structure and position of the dog and the human lung. Lantern demonstration followed.

Discussion.

DR. EWING: I have had opportunity to study the lungs in this case and found them highly interesting. The main feature was, as Dr. Wood describes, a remarkable desquamation of alveolar epithelium.

There were thrombi in many small vessels, and in many areas there were many heavily pigmented cells, such as are seen in the lungs of heart disease. Finally, there was, in my sections, quite a definite interstitial productive pneumonia. The characteristic lesions of the so-called bronchiolitis fibrosa obliterans, were missing. The epithelium of the larger bronchi was intact. It was difficult to reach a conclusion regarding the origin of the lesion and still more difficult to determine the exact cause of death. In this task the clinical history was not made available to me, but it was stated that the patient was in an advanced stage of chronic alcoholism. I would like to ask Dr. Wood if he observed in the lungs of his experimental animals the definite production of connective tissue and the collections of pigmented cells.

The general details of his experiments are also important, the method used in preparing the acid fumes, how close to the container the animals' nostrils were held, and how concentrated were the fumes. I performed some tentative experiments to determine the effects of inhalation of acid fumes on conscious animals, mostly guinea-pigs. I failed to produce any marked disturbance in guinea-pigs exposed to fumes of hydrochloric acid or nitric acid, under conditions reasonably simulating those to which the patient was said to have been subjected. I did not anesthetize the animals, but the fumes were so strong that tear fluid was instantly converted into foam and the animals struggled and snorted vig-

orously. On removal from the fumes, the animals promptly recovered and remained well.

DR. PHILIPS: This subject of nitric oxide poisoning is very interesting. I think in our service here in New York we rarely ever see these cases. Dr. Hudson, who has had an opportunity to see more of these cases clinically than anyone in this country, is here to-night, and I would like you to hear what he has to say.

DR. W. G. HUDSON: Dr. Hudson of the Dupont Powder Co. related some experiments which he had made with acid fumes. His conclusions based upon his experiments were as follows:

I. Injurious effects are due to the direct action of the fumes upon the lung tissues and not to changes brought about by absorption into the blood.

II. After a latent period of several hours there develops regularly, when the experimental conditions are properly arranged, an acute and usually fatal pulmonary œdema. Several animals which recovered later developed pneumonia.

III. No marked changes were found in the blood picture or in the coagulation time.

DR. BUTTERFIELD: If I understood correctly, the fumes of nitrogen tetroxide were really inhaled in these experiments, for, of course, nitric oxide cannot exist as such in the presence of oxygen. In the presence of water HNO_3 and HNO_2 would be formed from the NO_2 gas. One would, therefore, expect to find chiefly the combined action of acid (hydrogen-ions) and nitrite. The lesions in the lungs of the animals appear to be referable chiefly to the former. If nitrite formation occurs one would expect a most characteristic change in the blood, that is the conversion of oxyhamoglobin into methamoglobin. In fact one of the most convenient methods of preparing methamoglobin is to pass nitric oxide into the blood in the presence of oxygen.

A CASE OF FOREIGN BODY IN THE HEART.

C. H. BAILEY, M.D.

The organs exhibited were removed at autopsy from a patient who on entering St. Luke's Hospital gave a history of having been on a spree of five days' duration. Immediately following his dissipation he was seized with nausea and vomiting, and for five days all food taken was immediately expelled. He entered the hospital complaining of fever and muscular pains; the vomiting had ceased. His temperature ran an irregular course, ranging from 102 to 106. The white blood cell count rose from 22,000 on entrance to 34,000 two days later, with 85 per cent. polynuclears. A blood culture taken during his second day in the hospital showed *Streptococcus viridans* and *Bacillus coli communis*. The patient grew gradually worse, and died four days after entrance.

At autopsy the pericardium was found to contain 75 c.c. of unclotted blood. Protruding 1.5 cm. from the posterior tip of the right auricle was the end of an ordinary wooden toothpick. The other end could be felt within the auricle pressing against its anterior wall at the right auricular appendage. The wall of the pericardium where it was in contact with the protruding end of the toothpick was abraded but not pierced.

On the posterior wall of the duodenum, 14 cm. below the pylorus, at the point where it lay directly over the inferior vena cava, was an ulcerated area, 0.5 cm. in diameter. At the base of this ulceration there was a sinus, 1.5 cm. in length, leading backward and upward directly into the inferior vena cava. The anterior wall of the vessel in this region presented a rough eroded surface for about 5.5 cm. lengthwise of the vessel. The venous end of the sinus was closed by a small clot.

Nineteen cases in which foreign bodies were found in the heart have been reported in the literature, omitting the large number in which entrance to the heart was gained directly through the chest wall. Several of these cases gave a history of having swallowed the foreign body, but in none of them was a lesion demonstrated between the digestive tract and the venous system.

The present case appears to be unique in the demonstration of such a lesion.

The case will be reported in full elsewhere.

Discussion.

DR. FIELD: In considering this case I think that particular interest lies in the fact that cultures of *Streptococcus viridans* and *B. Coli communis* were found in the blood, as indicating the possible portal of entry for the viridans infection.

DR. BAILEY said that colonies of *Streptococcus viridans* were very numerous on the plates. Those of *Colon bacillus* were less numerous and it was feared that the latter might be a contamination. The autopsy findings, however, seemed to justify their presence in the cultures.

A COMPARATIVE STUDY OF THE WASSERMAN AND WEIL REACTIONS IN SYPHILIS.

CYRUS W. FIELD, M.D.

In 1906 in the *Journal of Infectious Diseases*, Weil described the occurrence of an increase in the resistance of red cells to cobra venom lysin in patients suffering from syphilis. A little later Schwartz reported on 600 cases in which he compared the Wassermann and the Weil reactions. This year Stone, of Toledo, reported another series; and Kuschucoff from Wassermann's laboratory has also reported a series.

Last spring we began a routine Weil test along with our routine Wassermann. We found that the Weil reaction was positive in 76% of primary syphilis, in 75% of secondary, in 73% of tertiary and 40% in questionable and negative cases and 50% in cases suffering from tumors, whereas the Wassermann reaction in the same series showed 70% positive in primary syphilis, 87% secondary, 75% tertiary and 30% in the questionables and

negatives. These figures are almost alike except that the Wassermann reaction gives a higher percentage in the secondary cases.

It was found that there were a few cases in which we obtained a positive Weil reaction in which there was absolutely no suggestion of syphilis or malignancy and we determined to run a series on absolutely normal individuals and so obtained the blood from eighteen of the internes of Bellevue Hospital for the Weil test. In sixteen of these cases enough was obtained to control it with the Wassermann. All sixteen were negative with the Wassermann. The two on whom there was no Wassermann test were both negative with the Weil reaction. In the other sixteen cases the Weil reaction was strongly positive in one, and a doubtful positive in two, negative in all the rest. None of these three individuals have any history, signs or symptoms which would indicate a specific lesion in either their personal or family history.

From our work with the Weil reaction it would seem to be of value in known cases of syphilis undergoing treatment and possibly where the Wassermann reaction could not be readily undertaken. The test itself is of very great theoretical interest as it shows that there is a distinct difference in the chemical constitution of the erythrocytes in normal individuals and in those suffering from syphilis and new growth. I do not think that one strong positive in eighteen is a fair number of positives from non-syphilitic individuals as it will give a high percentage, which would not be found if the number of cases were greater, though I do think that it will be found that the Weil test will give a larger proportion of positive results in non-luetic conditions than does the Wassermann.

Discussion.

DR. WEIL: I feel that Dr. Field has been rather too kindly in his treatment of me. He states that the cobra venom test was positive in three out of eighteen cases, which makes the percentage of error 16%. If it is present in 16% of other conditions,

then it should not be used as a diagnostic test under any conditions. I did not myself describe the resistance of cobra as diagnostic of syphilis, but as a very frequent accompaniment of syphilis. One may say that anæmia is very characteristic of late cancer, and still not maintain it to be a diagnostic sign. In fact, in my original paper, I described two "positive" reactions in individuals in whom it was gratuitous to suspect syphilis. Nevertheless, I believe such incidents to be rare exceptions to the rule that non-luetics do not react. Since my article was published in the *Journal of Infectious Diseases*, it has been taken up by several others who have attempted to show that it is almost diagnostic of syphilis, in the sense that it occurs in no other conditions. Until Dr. Field threw this bomb, I must say that I had been quite convinced by the evidence hitherto advanced.

Schwarz (*New York Medical Journal*, 1906, Jan. 6), gives a record of seventy-five cases of non-lues tested by the Weil reaction in which there was no positive reaction.

Stone, of Toledo (*Arch. Int. Med.*, July, 1912), gives a record of forty-three non-luetic cases tested, in which there was only one positive reaction.

Kuschakoff (*Ztschrft. fr. Immunitätsforsch*, XII, 5, 1912), who publishes from Wassermann's own laboratory, gives a record of from eighty to one hundred cases tested with both Weil and Wassermann reactions in which he showed that the resistance of sixty-seven undoubted luetic cases gave 15% more positives with the cobra venom test than did the Wassermann. In twenty-one controls he found one positive to cobra.

All of this evidence added together gives a record of one hundred and forty-nine cases in which lues had been excluded in which there were only two positive reactions. This result compares not unfavorably with the Wassermann, and is borne out by the further analysis of about five hundred cases, with the details of which I will not burden you, giving in all about 1.5% of error.

In summing up, I should say, as in my original paper, that the cobra test does not at present compete with the Wassermann as a reactive test. Cancer cases should be always excluded, as they

may give a positive reaction due to a general resistance, not to a specific one, as after injections of phenyl-hydrazine. In treated cases, old latent cases, and scarlets, the reaction may complement the Wassermann.

From a theoretical standpoint, as a bio-chemical reaction, the resistance to cobra seems to me to be of great interest. It is not specific, in the sense of antibody antigen reactions and could hardly be expected, therefore, to be absolutely diagnostic, like a Widal. But then, it is also true that the Wassermann reaction is not specific; it does not work with cultures of spirochetes, but does with ox hearts.

Discussion.

DR. FIELD: I have already said that the percentage based on the eighteen cases obtained from the Bellevue Hospital staff was not a fair figure. We also notice that Dr. Weil's statistics are the lowest, the next highest are those of Schwarz, and then Stone, which shows that the tendency has been to raise the percentage of the positive Weil reactions and establish it as a diagnostic reaction. Kuschuoff's one positive case among his control was a case of tuberculosis with no history or sign of lues.

A STUDY OF THE MALPIGHIAN BODIES IN A CASE OF SUB-ACUTE GLOMERULO-NEPHRITIS.

SAMUEL CLARK HARVEY, M.D.

(From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York.)

The histological details of glomerulitis* and their bearing on its mode of production have been the subject of much careful investigation and of a voluminous discussion extending over considerable time. There is yet lacking, however, any concordance of opinion and much may be accomplished by the consideration of the finer details in appropriate though isolated cases and their correlation with what is already known. It is in the hope of being of some assistance in this respect that this paper is written.

It is necessary to review briefly the literature bearing upon glomerulitis in order better to appreciate the important points to be observed in the description of the case reported. For a more complete consideration one is referred to articles by Löhlein,¹ Reichel² and Herxheimer.³

Changes in the glomeruli in nephritis had been previously described by Virchow, Beer, Johnson, Forster, Frerichs and others, but to Klebs⁴ belongs the credit for the first careful histological study used as the basis for an explanation as to the mode of production of the lesion. The essentials of his description are a swelling of the glomeruli, an increase in the number of cells lying within them and a lack of blood in the capillaries of the tuft. From this picture he reasoned a proliferation of connective tissue cells which are assumed to be present normally in small numbers between the vessel loops. This results in compression of the capillaries so that they no longer permit the flow of blood

*The term "glomerulitis" as first applied by Cornil and Brault⁵ to inflammatory changes in the Malpighian bodies is misleading, as has been pointed out by Herring.⁶ From the standpoint of derivation it does not include the capsular and pericapsular lesions. However, as it has come to signify all the changes seen in and about the glomerulus, and as we have no better term, it is used with this meaning here.

through the glomeruli. He also observed a slow proliferation and degeneration of the capsular epithelium but regarded this as of secondary importance to the vascular lesion.

The expression of this opinion immediately aroused interest in this problem and was soon followed by the publication of other papers describing various details and proposing numerous hypotheses. These may be in general divided into two main groups; the first agreeing with Klebs that the essential lesion is compression or blocking of the vascular loops; the second, maintaining that the varied aspects of glomerulitis are due to a quite direct toxic action on the various structural components of the Malpighian bodies.

Blocking of the vessels of the tuft may be brought about in one of three ways; from within, by the lodgment of emboli or the formation of thrombi; from without, by the thickening of the vessel wall; or by compression. Each of these three views has its advocates.

Thrombi in the vessels have been repeatedly observed (Langhans,⁷ Councilman,⁸ Klein,⁹ Nauwerck¹⁰ and many others), and the origin of these was for some time the subject of a quite animated dispute. Proliferation and desquamation of the lining endothelium (Litten,¹¹ Langhans,⁷ Welch¹² and others), blockage with cells transported there by the circulation (Ribbert,¹³ thrombotic and hyaline changes in the static blood (Langhans,⁷ Nauwerck¹⁰ and others), and the lodgment of bacterial emboli (Reichel,² Baehr¹⁴ and others), are the most important of the ascribed sources for such intracapillary masses.

Changes in the wall itself which have been held sufficient to occlude the lumen are hyaline degeneration and swelling of the endothelium and of the supporting framework of the capillaries (Herxheimer,³ Lyon¹⁵ and others).

Compression of the tuft vessels from without is the view which has been most frequently proposed. In the main, three methods of accomplishing this have been suggested; First, nearly all writers have noticed an increase in the number of nuclei in the glomeruli. Some have considered these to indicate a prolifer-

ation of connective tissue cells (Klebs,⁴ Langhans,⁷ Hanseman¹⁶ and others), other writers invading endothelial or epithelial cells (Cornil and Brault,⁵ Councilman⁸ and others), and still others, wandering cells from the blood. A sufficient degree of pressure may be exerted by the mere presence of a large number of cells, by the hyaline swelling and desquamation of those elements, or by the contraction of aging connective tissue.

A second method of producing pressure upon the glomerular vessels which has been suggested by several authors (Böhm,¹⁷ Goeman¹⁸ Tschitowitsch¹⁹ and others), is by an increase of connective tissue about the capsule which by direct pressure or by obliteration of the afferent artery at the base of the tuft produces the changes described.

Lastly, some assume proliferation and desquamation of the epithelial cells either of the capsule or of the tuft, or of both in such quantity that a direct compression of the glomerular loops is produced (Greenfield,²⁰ Chapman,²¹ v. Kahlden,²² Lyon¹⁵).

On the other hand, several writers (Löhlein,¹ Ophuls,²³ Herringham and Thursfeld,²⁴ Engel,²⁵ Fichera and Scaffidi²⁶ doubt the compression of these vessels by any of these mechanisms and describe them as filled with blood and capable of normal functioning. This being true, the proliferation and desquamation of epithelium, the hyaline changes and the cellular infiltration seen in the early stages are all the direct result of a toxic influence and show a varying preponderance of type depending upon the intensity and the duration of its action.

Aside from this problem, the nature of the "crescent" has been the subject of much discussion. Litten,¹¹ Marchiafavi and Volenti²⁷, and Greenfield²⁸ were among the first to make a careful study of this condition. Greenfield believed it to be a proliferation of the capsular epithelium and described it as of common occurrence in subacute and chronic nephritis and also as being present in many acute cases, especially in scarlet fever. Previously Klebs,⁴ Klein⁹ and Kelsch,²⁹ as well as others, had noted these changes in the epithelium but considered them of secondary importance.

Gaylord,³⁰ Tschistowitsch,¹⁹ and Engel²⁵ have called attention to the presence of small alveolar spaces in these bodies and the latter has suggested the following hypothesis as to the method of formation of the crescents. The toxic action causes a desquamation of epithelium which leaves denuded areas of capsule and glomerulus. These coming in contact adhere or a fibrinous exudate is formed which later becomes organized and the resulting adhesions covered with proliferating epithelial cells. He considers the entire process as strictly analogous to similar changes seen in serous cavities as described by Heinz³¹ and Grasen,³² and terms it "glomerulitis adhæsiva."

Herringham and Thursfield,²⁴ although they have confirmed Engel's observation question his interpretation. They believe that the different forms of these crescents represent varying stages of inflammatory exudation. The fluid having undergone solidification and containing desquamated epithelial cells, is pressed by the glomerulus into the peculiar shape observed.

The opinion that these are epithelial cells is by no means unanimous. The characterization of the lesion as a chronic or subacute condition and the observation of cases in the later stages has apparently influenced many to consider these cells as of connective tissue origin. Some difficulty has been encountered, however, in associating this idea with that of their intracapsular location and several ways have been suggested to account for this unusual position. Ziegler³³ and Recklinghausen³⁴ have suggested a metaplasia of epithelial into connective tissue and Böhm,¹⁷ Goe-man¹⁸ and Tschistowitsch¹⁹ that the membrana propria or the pericapsular tissue may send out processes. In addition to this Böhm describes actual rupture of the capsule and the subsequent invasion of the space through these gaps. Engel²⁵ and more recently Ophuls²³ think that these cellular masses represent but the end result of the organization of an inflammatory exudate.

Welch¹² and Lyon¹⁵ in the acute experimental lesion produced by cantharides have seen a massing of epithelial cells in the capsular space which they believe to be desquamated and regurgitated from the first portion of the tubule. Herringham and Thursfield²⁴ deny that these have such a derivation.

The case described is from the medical service of Dr. Theodore C. Janeway at the Presbyterian Hospital and from the pathological service of Dr. W. G. MacCallum to both of whom I am greatly indebted for the privilege of reporting it.

Clinical History: J. C. S. Male, aged 30 years. No possible cause of nephritis was elicited. Mother died of Bright's Disease. Two months previous to admission had had trouble with his eyes and a month later was told by a physician that he had kidney trouble with a high blood pressure. Two weeks ago began to have occipital headaches and stopped work; but has suffered continuously with them since. He noticed no œdema, but a week previous to admittance passed large quantities of urine. The physical examination was practically normal, with blood pressure varying from 160 to 200 mm. Hg. Two days after admittance the phenosulphonphthalein test gave a first appearance in one hour, and a total excretion of 22% in two hours. A day later, in the evening, puffiness about the eyes was noticed and the blood pressure registered 225 mm. Hg. He had passed no urine during the day and the next morning was totally blind. A venesection was done without any improvement and he continued to grow worse, passing but little urine. The blood at this time showed 0.153% of urea. The patient died seven days after admittance to the hospital. On entrance the urine showed a heavy trace of albumen with very many granular epithelial hyaline casts and some red blood cells. The temperature was normal.

The autopsy was performed by Dr. Lamb twelve hours after death and to him I am indebted for the clinical history as well as gross description. Nothing of note was found elsewhere than in the kidneys except for a moderate hypertrophy of the heart.

Macroscopical Examination: The left kidney weighs 210 gms. It measures $11 \times 5.5 \times 4$ cm. The capsule strips fairly easily exposing a surface showing pale reddish areas and a peppering with minute yellow specks. On one portion there is a considerable area of greenish discoloration extending a short distance beneath the surface. On section the cortex averages from 5 to 7 mm. in thickness. The striations are difficult to make out and

where seen are much distorted. The same yellowish points are seen throughout the cortex and the medulla. The pelvis and ureter are normal. On closer examination the surface also shows numerous irregular gray areas. The right kidney weighs 215 gms. and measures 13 x 6 x 4 cm. It is similar in appearance in all respects to the opposite kidney except that in the pelvis there are a few minute hæmorrhagic spots.

*Microscopical Examination.**—The larger blood vessels contain a small amount of blood. Their walls are not thickened and they do not show any hyaline change. The small vessels and capillaries in general seem somewhat distended with red blood cells. The arteries at the base of the glomeruli are wide open and in many instances can be traced well inside the tuft to the point where they break up into the capillary loops. Several of these are distended with blood, even in the Malpighian bodies in which the inflammatory changes, consisting of epithelial proliferation and hyaline degeneration in the tuft and capsule, are especially well marked. In every glomerulus at least a few loops may be found in which red blood cells are in an excellent state of preservation. In general, however, the greater the hyaline change the less the amount of blood in the tuft vessels. Spaces which appear to be capillaries containing no blood are frequently seen, and in an occasional one may be found granular material or swollen cells, but no thrombotic masses are made out. That such an appearance may be caused by lymphatics or capillaries cut obliquely or longitudinally seems entirely possible if one bears in mind the difficulty with which observations are made in such a minute and complicated structure as the glomerulus.

*The microscopical examination was made with specimens fixed in Zenker's and in formalin. Mallory's aniline blue connective tissue, Mallory's iron chloride hæmatoxylin, Van Gieson's, Sudan III, and hæmatoxylin and eosin were the stains employed. The first was found to be by far the most satisfactory, especially when the acid fuchsin was omitted, since it enabled one to follow the connective tissue and hyaline in great detail.

Too much emphasis cannot be laid upon the necessity for examining such material in serial section. The appearance at different levels in any given glomerulus may be very different and a single section often gives a quite inadequate and erroneous idea as to the changes which have taken place. This microscopical description is based upon such an examination.

The number of nuclei in the glomeruli is not increased if one is careful to rule out those epithelial cells lying between the loops and in the crevices of the tuft. A great majority of the intraglomerular cells have large round or slightly oval nuclei in which the loose network of chromatin stains sharply. In the more hyaline of these the chromatin tends to be massed to a greater extent at the periphery of the nuclei. No mitoses are observed in these cells. The cell outline is exceedingly variable, being occasionally circular, more often oval or drawn out in a lanceolate form. The cytoplasm takes the eosin stain in some instances quite brilliantly, in others more faintly and with Sudan III, in many, droplets of fat are found. In a few glomeruli these cells appear to be fused together in hyaline masses, and here the nuclei are comparatively infrequent. An occasional polymorphonuclear leucocyte or a small round mononuclear may be found and now and then a plasma cell. However, the great majority of the cells seem to correspond to the endothelial type.

The most striking change apparent in the glomeruli is the presence of a large amount of intercellular tissue which takes an intense blue with Mallory's connective tissue stain. The substance is not at all fibrillar and seems to lie with respect to the vessel loops in the same position as the membrana propria of an epithelial membrane. With hæmatoxylin and eosin the entire intercellular substance of the glomeruli seems to stain varying degrees of red and quite intensely in many places. The cells in those tufts showing the greatest change from the normal also stain a bright red and seem to fuse with the intercellular substance so that the whole has a homogeneous appearance. Such masses of fused endothelial cells may be easily taken for hyaline thrombi in the capillaries, but no such appearance is found with Mallory's stain.

At the base of the tuft the pericapsular tissue does not seem in any considerable degree continuous with the intercellular material of the glomerulus and there is no disproportionate increase in the hyaline material at this point. The epithelial cells covering the glomerulus are supported on a hyaline membrane which resembles that lying beneath the endothelial cells of the

capillaries. The connective tissue fibers passing across the capsular space with the adhesions, apparently do not invade this membrane but seem only attached to it.

The epithelial cells covering the glomerulus and dipping between the folds of it are of an irregular and somewhat flattened cuboidal type. The nuclei are large, oval and vesicular and no mitoses are observed. The cytoplasm is highly granular and in some cells large droplets staining a blue or in a few instances a bright red with Mallory's connective tissue stain are seen. With Sudan III fat droplets now and then are observed. It is only occasionally that these cells are piled upon each other and it is impossible to say whether those seen lying loose in the capsular space are of glomerular or of capsular origin. In places where there are adhesions between the capsule and the tuft the epithelium is continuous over the surface of the adhesion as far as the proliferating capsular type into which it gradually merges. In the very advanced stages of hyaline change in the glomerulus these, as well as the intraglomerular cells, are few in number and degenerating.

The capsular epithelium in a great majority of instances shows some degree of proliferation, varying from a layer two or three cells deep to the crescent shaped masses which are so characteristic of this type of kidney. These cells approximate very closely in appearance those lining the glomeruli. They are large and cuboidal in shape, slightly oval and vesicular, with a sharply staining network of chromatin. No mitoses are observed although two or three cells are seen in which two small nuclei are present, and a few others in which the chromatin is grouped in larger masses and takes the hæmatoxylin more intensely. The cytoplasm is finely granular and only in the late stages of the lesion does it show marked degeneration. It is apparently only when these cells become detached that fatty or hyaline droplets are seen within them.

When these proliferating cells form masses more than two or three layers deep a careful study under high magnification of a section stained with Mallory's connective tissue stain shows the following condition. The whole appears to be made up of

numerous branching and redundant processes lined with epithelial cells which seem to have toppled over upon each other and to have been crushed together. Where the masses are of looser consistence many minute spaces may be seen which intercommunicate and are bounded by these outgrowths of epithelial cells carried upon a fine supporting stroma. Peripherally this structure is attached to the swollen and hyaline basement membrane of the capsule, but centrally it rarely reaches or adheres to the glomerulus. There is, practically always, at least a potential capsular space internal to the "crescents" and broken across only by adhesions which are quite different in structure from the latter.

Such masses of proliferating cells as a rule appear crescentic only when cut in a plane parallel with the stem of the tuft and if the section is at right angles to the latter, the glomerulus lies in the center completely surrounded by masses of capsular epithelium. The proliferation usually stops rather abruptly at the entrance of the tubule, but now and then strands of cells project into it for a short distance. Many desquamating epithelial cells apparently derived from the Malpighian body are found in the tubules near their parent glomeruli.

In many tufts masses of fibrous tissue extend from capsule to glomerulus and these may cover as much as a third of the circumference of the latter, or on the other hand consist of thin and threadlike bands. In this manner the capsular space may be split up into several smaller cavities which are intercommunicating and eventually open into the space leading to the tubule. These are all lined with epithelium and contain only an occasional desquamated cell. Peripherally the adhesions appear to be directly continuous with the pericapsular connective tissue through gaps in the membrana propria, but centrally they seem merely attached to the intercellular substance rather than in direct continuation with it.

The pericapsular connective tissue as well as the membrana propria is swollen and stains quite intensely blue with Mallory's connective tissue stain. An actual increase in the amount of connective tissue does not appear in the sections cut through the

center of the glomerulus. A deceptive appearance is obtained in those sections passing through the pericapsular tissue only, which may cause one to suppose a great increase in connective tissue, but examination in serial section corrects this view. A slight increase is found at the point of origin of the adhesions and once or twice a small blood vessel is seen to pass into the glomerulus at such a place. The membrana propria is interrupted at several points where there are no adhesions but as yet invasion of connective tissue through such gaps cannot be seen.

Many of the tubules are filled with homogeneous or faintly cellular hyaline casts and some of them are dilated. Occasionally red blood cells are seen in them and also desquamated glomerular or tubular epithelium. The lining cells are swollen, especially those of the convoluted portion and many of them contain fat and a few large hyaline droplets. The interstitial tissue is quite œdematous and in places infiltrated with small round mononuclears and plasma cells but there are only a few polymorphonuclears present. The connective tissue seems more prominent than normal, perhaps because the fibers are separated by the increase in interstitial fluid.

Discussion.

Before discussing the significance of this case and attempting to correlate the findings with the observations and opinions of others, it is necessary to decide quite definitely its position among the various forms of glomerular lesions. Among those forms of nephritis in which the glomerular changes are prominent there are two types which must be sharply distinguished from the one described above.

The work of Lenhartz,³⁶ Löhlein,¹ Gaskell,³⁷ and Baehr¹⁴ has defined quite clearly a form of glomerulo-nephritis associated in many instances with subacute or chronic endocarditis and in which the *Streptococcus viridans* (Schottmüller) seems to be most frequently the etiological factor. To quote Baehr:⁴ "The salient features of the pathological picture are first, the involvement of one or more loops of a variable number of glomeruli;

secondly, the absence of any visible disease in the uninvolved glomeruli, and in the uninvolved portions of affected glomeruli; thirdly, the association in most of the bacterial cases of all the various stages of the glomerular process often seen in a single microscopical section." The inability to distinguish this type from the true toxic glomerulo-nephritis in which typical crescent formation is found has led to great confusion and erroneous conclusions. A toxic influence affecting the entire Malpighian body is quite a different process from the lodgment of emboli of bacteria in certain loops of some glomeruli, although as Ophuls²³ has stated the fundamental lesion in both types may be chronic sepsis. At least one instance of such confusion may be cited, namely that of the report of Herringham and Thursfield²⁴ dealing with the formation of "crescents" in which a plate shows typical changes of this embolic type. It is also possible that the thrombi as frequently described in the glomerular vessels have been of this derivation.

Quite a different lesion is that of the second type which must be differentiated from the one described here. It is dependent upon changes in the arterioles of the kidney, frequently accompanied by similar lesions of the small vessels of the brain, spleen or elsewhere. Such changes in the kidney were originally described by Gull and Sutton,³⁸ and have been more recently investigated by Jores.³⁹ There should be no confusion with this form in which the picture is merely one of hyaline change and fibrosis of the glomeruli with no epithelial proliferation. It is obvious that deductions drawn from a glomerulo-nephritis of this type cannot be applied in general to all glomerular lesions or specifically to such as the one reported above with any hope of arriving at correct conclusions.

Furthermore, within this one type confusion may arise from the failure to differentiate between various stages of the lesion. Thus, in the early glomerulo-nephritis one finds the tuft filled with cells of an endothelial type or with wandering cells from the blood, so much so that the capillaries have the appearance of being compressed, and one is tempted to consider this factor as the cause of the lesion seen later. Again, a careful study of the

capillaries in the more acute stages shows, as has been emphasized by Langhans,⁷ the presence of thrombi of cells and of fibrinous and hyaline material in the capillaries of the tuft, which also would seem capable of bringing about serious changes. It must not, however, be forgotten that these are the accompaniments of an acute inflammation and probably do not play a prominent part in the later stages.

This kidney is classed as belonging to the subacute stage of a toxic glomerulo-nephritis which according to Löhlein¹ ultimately terminates, if death or resolution do not occur, in a nephro-cirrhosis secundaria (Aschoff⁴⁰). Crescent formation is characteristic only of this form of nephritis (Gaskell³⁷).

Inasmuch as the picture here is not obscured by acute inflammation or excessive repair it should be possible to determine which factors in the development of the lesion are essential and permanent and which are incidental and temporary.

Is then the obliteration of the blood vessels as described by so many authors a permanent and causative factor? As noted in the description, every glomerulus contains some capillaries which are filled with blood and the number of such vessels is as great or greater than that seen in the glomeruli of several normal kidneys examined. In fact this appearance is normally so variable, that the lack of blood in a tuft is of questionable importance. Its presence, on the other hand, is positive proof of the patency of the vessels in question. The arteries at the base on examination in serial section can be followed into the tuft to the point where they break up into smaller branches and in most instances are wide open and filled with red blood corpuscles. This is true even where the hyaline degeneration and epithelial proliferation is most pronounced. Reichel,² Fichera and Scaffidi²⁶ have called attention to the same normal appearance of the blood vessels in this condition. The latter states: "in den weiter vorgeschrittenen Fällen in denen der Kapselraum fast ganz oder vollständig gefüllt, eine wirkliche kompression der Gefässchlingen nicht zu sehen war; in Gegenteil zeigten letztere auf einen Querschnitt deutliche durchgängige, mit roten und weissen Blutkörperchen

gefüllte Lumina, wie gewöhnlich mit freien Lücken zwischen den einzelnen Blutkörperchen." It does not seem probable then, that the glomeruli of this type of nephritis suffer from an insufficient blood supply or that the lesion is due to such a deficiency. If they have so suffered in the past, it is hard to understand how lesions so severe as the ones noted by many writers could take place with no permanent injury to the circulation, and yet bring about so profound a change as is seen in the glomeruli of this case.

Furthermore, no increase in the number of the cells within the tuft is found here. Either it was never present, or as seems much more probable considering the uniformity of opinion of various writers on this point, the occurrence and influence was but temporary. Thrombotic masses within the vessels were also looked for with special care, but not found. That they are a quite constant accompaniment of the earlier stages of glomerulo-nephritis can not be doubted from the frequency with which they have been observed. Löhlein² suggests that in the course of time these are absorbed or in some other way disposed of, which would seem to be the case here. It must be concluded that these likewise are but a temporary, and not an essential factor in the production of the later lesions of this form of glomerulitis.

The presence of connective tissue within the tuft is not proven in this case. The material staining a deep blue with Mallory's connective tissue stain is not fibrillar but quite homogenous, has apparently no connection with the pericapsular connective tissue at the base of the tuft and appears as a greatly thickened and swollen membrana propria of the capillary loops. Although such a basement membrane is not readily seen in connection with the capillaries of the glomeruli, it is possible that the hyaline changes serve to make it more easily distinguishable. Many masses of connective tissue which at first glance were taken to be glomeruli having undergone a fibrosis, are found, on examination in serial section, to be merely masses of pericapsular tissue at one pole of the Malpighian body. It is probable that these hyaline glomeruli are organized and converted into connective tissue as seen in the very late stages of contracted kidney, but such changes do not

show in this case. The small amount present makes it improbable that the overgrowth or invasion of such tissue with consequent contraction can have any primary effect in the production of the picture seen here.

The last source of the possible obliteration of the blood vessels is from the abnormal growth of the epithelial cells. In the great majority of the glomeruli studied, there is a definite space between the proliferating capsular cells and the tuft as well as numerous spaces in the mass of epithelium. Such an appearance combined with compression of the glomerulus can only be imagined on the supposition that the tubules leading from the Malpighian bodies are obstructed. Although in several instances strands of epithelial cells were found lying at the point of origin of the tubule, in no case was this condition sufficiently great to block the egress of the fluid. Since the glomeruli always show some blood, it cannot be supposed that the tuft is compressed in all directions as would be the case according to this hypothesis.

This same argument will apply with equal force to the supposition that pericapsular connective tissue may compress the glomeruli by overgrowth and contraction. Constriction of the vessel at the base of the tuft by such growth was in no instance observed, although the vessel could, in most glomeruli be followed to the point of its branching into the tuft vessels. The assumption of Böhm¹⁷ that an increase of connective tissue and a resultant contraction causes such a compression because of its greater condensation at the junction of the glomerulus with the capsule is not found to be true. He pictures the fibers as running over the capsule downward to the base of the tuft where consequently they seem relatively increased. The shortening of fibers running in this direction would not tend to constrict but rather to distend the neck of the glomerulus and consequently the enclosed vessels. To have the effect proposed they should be arranged in an annular manner about the neck and such an arrangement we have not seen.

Thus it seems that the essential changes are hyaline degeneration of the connective tissue and membranæ propriæ, and epi-

thelial proliferation, rather than interference with the blood supply of the glomerulus and increase in connective tissue.

There are two common causes assigned for the production of hyaline degeneration*—the lack of proper nutrition, and the action of some toxic influence. It is of course possible that here the blocking of the vessels, as previously described, in the more acute stages is sufficient to produce this change. But we know that this condition is not maintained and one would expect on removal of the causal factor a rather prompt restoration to the normal. It is more reasonable to agree with Löhlein¹ that this is the result of a long continued toxic action and of somewhat the same nature as that which leads to a production of amyloid.

Herxheimer,³ in a study of hyaline change in the glomerulus and capsule, has found it to start in the inner layer of the membrana propria and in this case the same structure shows the most profound change. Such an alteration cannot but have an important effect upon the epithelium which rests upon it. Whether this actually results in the proliferation which is seen in these cases or whether, as Herxheimer thinks, the reverse is true, cannot be definitely answered until the lesion can be produced experimentally and every gradation of it carefully watched and timed.

Within the capsular space two quite different and distinct phenomena are observed. The most constant and pronounced is the proliferation of the epithelium lining the capsule. Careful study in serial section convinces one that these crescentic masses consist of cells lying upon a supporting stroma which projects in folds and tongue-like processes, exceedingly redundant, into the capsular space. Here they are pressed to one side by the glom-

*By the term hyaline degeneration is meant a swelling and homogeneous appearance of the connective tissue and the membrana propria, and the tendency to take the blue in Mallory's stain with intensity. No definite micro-chemical reaction is implied by the use of this name. Indeed, it seems probable as Oplund² has pointed out, that it is impossible to distinguish this from the beginning of amyloid infiltration, or, on the other hand, from the changes which are not sufficiently marked to be called hyaline.

erulus as it expands and contracts under the varying blood pressure until they ultimately become packed in a stratified mass about the tuft.

That these proliferating cells are of epithelial origin can not be doubted. Their shape, size and arrangement upon the supporting stroma confirm this idea and there is no occasion to invoke the aid of metaplasia to explain their presence.

One cannot hold the idea of Herringham and Thursfield²⁴ as well as of others that these are but desquamated cells caught in a solidified exudate and pressed to one side by the expanding glomerulus. These cells attached to a definite stroma and showing no signs of degeneration are alive, and as far as can be judged from the microscopical examination, are in quite a normal condition.

It is true that mitoses are not found, but this is of slight negative importance. Gaskell,³⁷ Arnold and Baumgarten,⁴¹ Crooke,⁴² Löhlein¹ and others have noted their occurrence in similar cases as well as the presence of cells with two or more nuclei. Fichera and Scaffidi,²⁶ because of their inability to find mitotic figures and because of the occurrence of such multinucleated cells, conclude that cell reproduction takes place amitotically as has been noted in the cornea (Ranvier) and in the skin (Marchand). Such an explanation is hardly necessary, however, as those cells which contain more than one nucleus, are in our preparations, at least, degenerating and probably conform with the condition of a typical cellular division as seen by Lambert¹³ in cells growing in vitro.

This process of proliferation greatly resembles and apparently is analogous to certain lesions seen elsewhere. Thus in the thyroid gland in exophthalmic goitre (MacCallum⁴⁴), the cells lining the alveoli of the thyroid increase enormously in number and form redundant and manifold trabeculae. Also in chronic cystic mastitis, in hypertrophy of the prostate, in coccidiosis in the rabbit's liver (Tyzzer¹⁵) and in many adenomata a similar appearance is found.

This epithelial proliferation must be sharply distinguished

from the second change observed in the capsular space. This is the formation of adhesions as described by Goemans¹⁸ and Engel.²⁵ The mode of production is very different and it is the attempt to apply deductions based on this form to the epithelial proliferation that has led to considerable confusion.

One can best conceive of the formation of these if the capsular space is thought of as being analogous to other serous cavities, as has been suggested by Engel and others. The desquamation of the lining epithelium in the acute stage leaves exposed the underlying capsular and glomerular surfaces. When these come in contact they tend to adhere, or between two such exposed points fibrous bands may be formed. These latter become organized and covered with epithelium, thus splitting the glomeruli into two or more spaces. These spaces are open and communicating with each other and also with what is left of the capsular space, thus ultimately emptying into the tubule. These cavities are in no sense cysts as has been erroneously stated. Such adhesions may be so extensive as to fill a third or more of the capsular space and render the distinction between glomerular and capsular tissue somewhat difficult to make. In some instances the organization is so complete that a small blood vessel may be seen running through such a band to the glomerulus as was first noted by Greenfield.²⁸

It is in such a formation as this that Böhm,¹⁷ Goemans¹⁸ and Tschistowitsch¹⁹ find reason to suppose that the capsular space is invaded by connective tissue. Such a condition as far as has been seen here only takes place in the organization of these adhesions.

The future of the proliferated cells and the manner in which the glomeruli become converted into connective tissue and hyaline masses, as seen in the secondary contracted kidney, can not be predicted from these observations. Such gaps as have been described by Böhm¹⁷ in the membrana propria have been observed and it may well be that the crescentic masses ultimately become organized by the invasion of connective tissue through such places or converted into hyaline masses in the manner proposed

by Herxheimer.³ However, such processes follow and do not precede the epithelial proliferation.

Summary.

(1) Obstruction of the blood flow through the glomeruli is not essential to the production of the lesions in the Malphigian bodies.

(2) Cellular infiltration of the glomeruli and thrombi in the glomerular vessels are temporary and do not result in the late lesions.

(3) The characteristic and more essential changes are:

A. Hyaline degeneration of the membrana propria of the capsule and of the walls of the glomerular capillaries.

B. Proliferation of the capsular epithelium in the form of an exceedingly redundant membrane with compression of it into the characteristic "crescents."

C. The formation of adhesions between the capsule and the glomeruli, i.e., the "glomerulitis adhesiva" of Engel.

(4) The increase of connective tissue in the Malphigian bodies is slight, and consequently is not concerned in the production of the changes observed.

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ILLUSTRATIONS.

- FIG. 1.—The glomerular capillaries contain considerable blood and the arteries at the base can be followed into the tuft. Mallory's aniline blue: x625.
- FIG. 2.—Marked hyaline change in the tuft and membrana propria of the capsule. Proliferation of the capsular cells upon a supporting stroma. Mallory's aniline blue: x625.
- FIG. 3.—Proliferating cells lining the capsule and forming an exceedingly redundant membrane. Mallory's aniline blue: x1000.
- FIG. 4.—An adhesion between a glomerular loop and the capsule, with formation of a redundant capsular membrane. Mallory's aniline blue: x1000.

Discussion.

DR. MACCALLUM: I have been interested in the study of this case of glomerulo-nephritis, because I, myself, have never been able to see the formation of crescents from desquamated epithelium in the capsule of the glomeruli just as is pictured in all the text books. Is that condition familiar to any of the members?

Even those kidneys which have suffered alteration in consequence of septic infection and exanthematic diseases seemed to show, too, the same condition as found in this case where the cells are by no means desquamated but rather portions of an actively proliferating tissue.

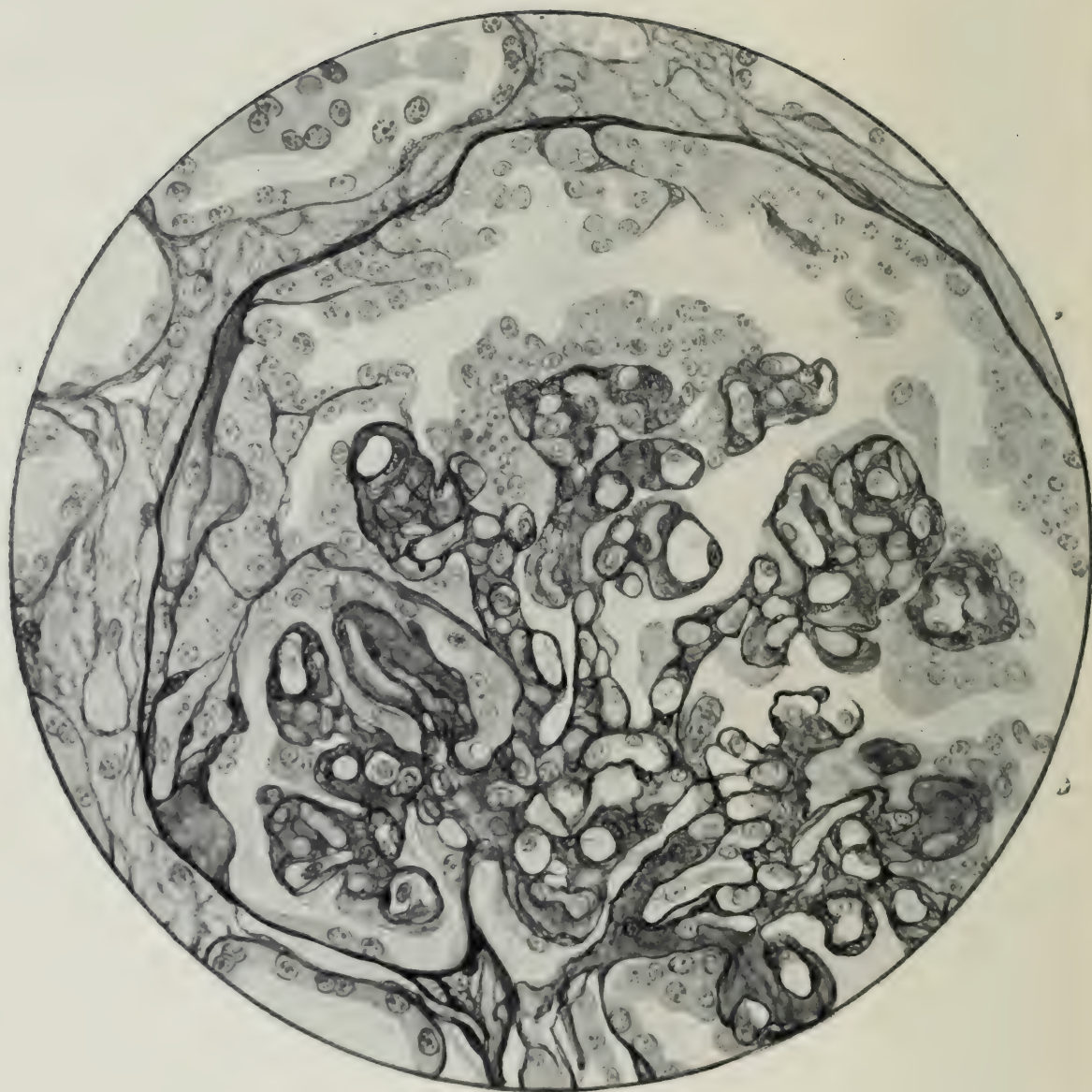


FIG. 2.

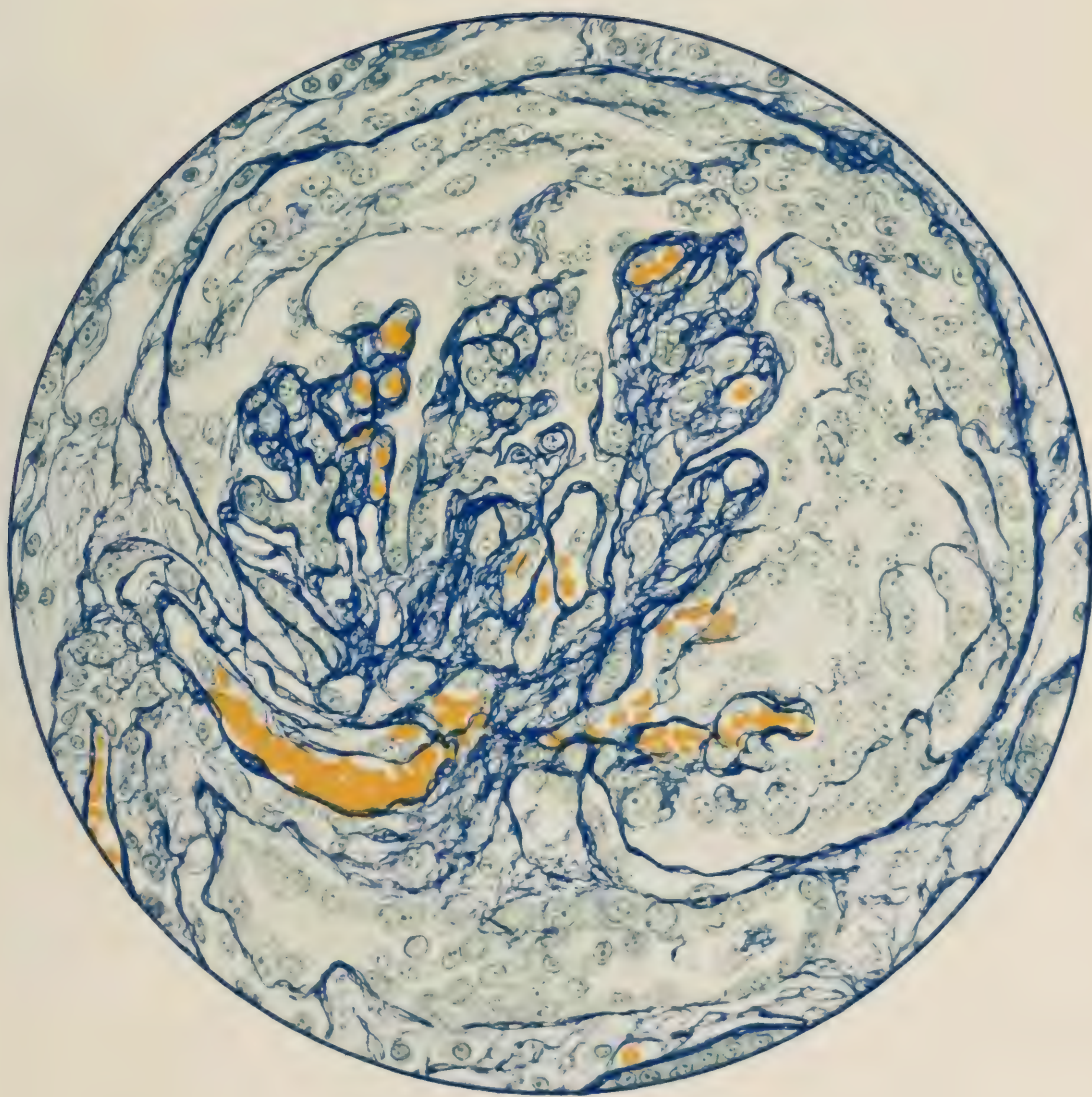


FIG. 1.



FIG. 3.



FIG. 4.

THE STRUCTURE OF THE SPLEEN AND ITS RELATION TO PATHOLOGIC PROCESSES.

Dr. Morris' report based on the work of Maximow, Weidenreich, Mollier and others and upon his own study of the spleen in various forms of acute splenic tumor tended toward the acceptance of their views that the essential cells of the splenic pulp are of the same character as the endothelial cells lining the sinuses, and that from these there may be developed independently all of the numerous types found in the bone marrow and thus ultimately those cells which circulate in the blood. This myeloid transformation of the spleen is exaggerated in infections and intoxications with the production of the acute splenic tumor, but is recognizable also in the normal spleen.

In the more severe infections, polymorphonuclears appear in great numbers, while in milder forms other types such as the myeloblast and myelocyte are predominant. The interruption of the original cell connections in the production of these new cells adds greatly to the softening of the spleen.

A detailed account of this work will be published later and elsewhere.

Discussion.

DR. STEWART: Might not the accumulation of myelocytic cells be explained otherwise? We know, for instance, that in certain infectious conditions myelocytes are stimulated and may be found in other organs of the body.

It is possible, then, that we are dealing merely with a transportation of those cells in the spleen and not with a new formation.

DR. ORTEL: What, from your own observation, is the process of transformation of the nucleated red blood cells into the non nucleated type?

DR. MORRIS: The nuclei become pycnotic and fragmented and the nuclear fragments are extruded into the surrounding blood plasma.

DR. MACCALLUM: I think that there is danger in claiming the origin of one cell from another merely because they lie side by side and intermediate forms can be seen. For this reason Dr. Stewart's objection must be carefully considered.

At the meeting of the German Pathological Society in Strasburg, a kidney was shown in which a large area in the tissue about the pelvis was proved to be composed of bone and marrow elements and the development of bone marrow in other regions quite apart from the skeleton has long been recognized. Nevertheless the appearance of bone marrow cells scattered through the spleen may possibly have another explanation than that they are produced directly by the spleen. That it is different in different processes may be seen by the comparison of acute splenic tumor in pneumonia with that in typhoid.

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DR. W. G. MACCALLUM, *President.*

CASE OF MULTIPLE MYELOMA.

DRS. CHARLES NORRIS AND B. MORGAN VANCE..

Dr. Norris presented briefly a case of multiple myeloma. The organs came from a man 54 years of age, a window dresser by occupation, who entered the service of Dr. Draper at Bellevue Hospital on January 26th, and died October 20th of the present year. Seven months before admission he complained of stiffness and tenderness in the neck and ribs; the pain increased rapidly so that in the next two months he was forced to go to bed. The pain was worse on movement. A week before his death he developed pneumonia from which he died.

The body was poorly nourished, 176 cm. in height. The arms and legs show extreme emaciation; skin is pale and of fine texture. The lungs are everywhere congested and slightly oedematous; the upper right lobe is in a condition of red hepatisation. The kidneys are large and congested. Spleen is somewhat small and fibrous. The other viscera show but little change from the normal. The sternum is thickened, soft and everywhere infiltrated with white and red tumor tissue. The ribs show numerous large and small, mostly fusiform, swellings, the largest about 3 inches in length. The tumor infiltration in the ribs is very extensive. The clavicles are also infiltrated in places with tumor tissue. The cervical vertebrae are soft, are easily penetrated with the point of a knife, and there is a considerable amount of tumor tissue which has grown through the periostium of the vertebra forming a flat mass of yellowish white tissue in front of the upper cervical vertebrae. The basilar portion of the occipital bone is softened and can be readily cut away with a knife. The lower end of the right femur shows a focus which is dark red in color; otherwise the bone marrow is normal. The upper half of the left femur is extensively infiltrated with tumor tissue with large hæmorrhagic-like areas. A few of the dorsal vertebrae examined show small tumor areas.

The microscopic examination of the viscera shows but slight changes besides those mentioned above. There are, however, recent areas of focal necrosis of small size in the spleen and the muscle of the anterior abdominal wall shows a well marked hyaline degeneration. Examination of the sections taken from various portions of the bone infiltrated with tumor growth shows that the tumor is made up of two kinds of cells—a large cell with protoplasm in which no granulations can be made out, with a large nucleus occasionally eccentrically placed with a definite nuclear membrane and with scanty chromatin network. The other cell is smaller in size with a dense, small, deeply staining nucleus and with a markedly eosinophilic protoplasm. The tumor cells are free and there is only a very scanty amount of reticulum. Dr. Norris came to the conclusion that these latter cells were

erythroblasts and that the two types of cells were derived from cells analogous to the primitive blood cells of Maximow. Smears made directly from the fresh tumor and stained show no granulations. Examination of the tumor cells in the hanging drop likewise show no granulations. During life the urine contained very large amounts of Bence Jones protein. A full description of the clinical history and the microscopic findings and conclusions will be published elsewhere.

Discussion.

DR. EWING: I think that the classification of the tumors according to cell form meets with difficulty, since the cell forms seem very different in various tumors. I have seen one tumor of a plasma cell type in which the plasma cell characters were very distinct. In most of the tumors, however, the cells resemble neoplastic marrow cells of various types, as in Dr. Norris' present case.

The early authors were too narrow in their conception of tumors primary in the bone marrow. Many of the typical cases show Bence-Jones protein in the urine. Cases of metastases have later been added to the group and the tendency has been steadily to enlarge the scope of tumors originating from bone marrow cells. These cases present every degree of malignancy, and a wide scope for this disease must be recognized, since there is such a wide divergence of the cells from which the tumor can arise. Dr. Norris' case seems to have originated from the mother cells of the leucocytic series.

I have recently had opportunity to study the literature and have reached the same conclusion as Dr. Norris on the subject. The plasmomata illustrate the difficulty in distinguishing between the neoplastic and inflammatory nature of these growths.

DR. MACCALLUM: I once described a case of myeloma in which the cell presented a different appearance from those in the case which Dr. Norris has just shown. The nuclei in his case are much smaller, the nucleated red blood corpuscles are more numerous and the cells are more typical of the plasma type than were those in mine.

DR. EWING: Was there any particular distribution of the nucleated red blood cells and did they show neoplastic characters? Is it not possible that they may have been merely normal marrow cells which had become included in the tumor?

DR. NORRIS: The drawing shown comes from the prevertebral tissue in the neck which is distinctly tumor tissue and not bone marrow tissue. There are very few red blood cells, especially in the specimen from which the drawing was made.

DR. MACCALLUM: A specimen which was given me by Dr. Norris from the case was stained by Miss Kirkbride to demonstrate cell granules, but none were shown. The cells also gave no oxidase reaction.

ANOMALY OF THE INFERIOR VENA CAVA WITH THROMBOSIS.

W. G. MACCALLUM, M.D.

D. F., a man aged 28, who had previously been in good health, entered the Presbyterian Hospital in the service of Prof. Janeway on September 20, 1912, complaining of pain in the anterior and inner sides of his left thigh, with a lump in the groin. This was treated by massage. During his stay in the hospital his temperature was moderately high. There was a leucocytosis with increased percentage of polymorphonuclear leucocytes. Widal test negative as were blood cultures. There were clinical evidences of thrombotic obstruction of the veins of the lower extremities and pelvis. There was some oedema of legs and feet. Toward the end of his life, there were the physical signs of a lobular pneumonia.

At the autopsy (Autopsy No. 8202) performed by Dr. MacCallum, there was found the following condition. The legs were not noticeably oedematous but firm cords could be felt in the posi-

tion of the great veins in the thigh. The peritoneal cavity contained no excess of fluid and the organs were normally disposed except in that the common iliac veins with all their pelvic and femoral branches were distended into firm masses and surrounded by dense adhesions. The inferior vena cava was only slightly embedded in such adhesions but was similarly distended and firm up to a point near the level of the renal veins. On being opened from above it was found to be filled by a brownish red thrombus which ended rather abruptly about 2 cm. below the renal veins. Below this point it completely occluded the vena cava and a similar complete occlusion could be observed in the common, internal and external iliac veins and in practically all their branches in the pelvis. Both femorals with their saphenous branches were occluded as far as they could be traced. The thrombus, especially in the femoral and pelvic veins was somewhat softened centrally, of a dark rust red color and quite intimately bound to the vein wall.

The ascending lumbar veins were open and contained fluid blood. They were extremely wide and the left had worn a wide channel in the bone along the side of the vertebral column. A probe passed through them entered the enlarged right azygos vein. Just below the openings of the renal veins there was, in the posterior wall of the vena cava, an orifice about 1 cm. in diameter through which the cavity of the vena cava communicated with that of the enormously enlarged right azygos vein. This canal, which was very thin walled, could be readily traced to its opening into the superior vena cava and through most of its course was found to measure about 17-20 mm. in diameter.

The renal veins appeared to be normal but above them the vena cava was relatively narrow, measuring about 15 mm. in diameter. It ran upward behind the liver to empty together with the portal vein into a common sinus, from which the branches normally forming prolongations of the portal vein only ran into the liver. The portion of the inferior vena cava extending from the liver to the right auricle appeared normal and the openings of the hepatic veins into it were normally arranged, but a probe

passed downward in the direction of the post hepatic portion of the vena cava entered a rather narrow canal, which rapidly narrowed until it became a solid cord, the tip of which approached the remainder of the inferior vena cava as it opened together with the portal vein into the liver.

Evidently this complete obliteration of the inferior vena cava in its passage behind the liver was primary to the development of the extraordinary collateral venous circulation described. It must be thought that the blood of the inferior vena cava passed to the heart largely by way of the vena azygos, but there was also the possibility that it might pass with the portal blood through the capillaries of the liver. On the other hand, some of the portal blood may have sought out the rather easier passage to the heart by way of the azygos, especially since its tension is normally higher than that of the vena cava. This factor, as well as the roundabout path presented to the blood, must have caused a very considerable obstruction to the outflow from the vena cava, and this probably constituted the important predisposing factor in the development of so extensive a thrombosis of the veins of the pelvis and lower extremities described.

These conditions are made clear by the drawing Fig 1.

Fig. 2 is a diagram of the development of the veins in so far as they are concerned in this case, which we have made under the direction of Dr. Huntington, whom I thank for it. It shows that the inferior cava is produced in different ways in its various segments, for while the uppermost part arises originally from part of the vitelline veins, that part which traverses the liver is like the branches of the portal and of the hepatic veins, crystallized out from the original plexus of veins or sinuses into the meshes of which the liver diverticula grow. Consequently, it is easy to see how this foreshadowed condensation of the sinuses along a certain path, into one trunk might be interrupted as at (A), while it is equally easy to understand that a connection with that group which becomes the intrahepatic portal might persist, although usually obliterated as at (B). From the liver the condensed path of the future vena cava forms connections which are

normal in this case, with the subcardinal plexus, and through this with the complex and frequently changing plexus of supra- and post-cardinal veins which finally form the lower part of the cava. In this case the original wide connection of the post-cardinal vein which forms the azygos seems to remain. The vertical line of somatic anastomosing branches which come to form the ascending lumbar veins equally retain their connection with this azygos vein.

On the whole we have, as it appears, a failure in the coalescence of sinuses high up in the hepatic plexus to form the vena cava inferior at that point. Below this its formation is perfect enough but it retains some of its original sinus connections and thus empties into the portal trunk. The persistence of the azygos connection is evidently secondary and establishes the collateral circulation from the lower regions.

Discussion.

DR. EWING: Was there in this case any disturbance in the portal circulation?

DR. MACCALLUM: The clinicians noted only the thrombosis and pneumonia. There could not, therefore, have been any great disturbance in the portal circulation. The condition might have caused dilution of the blood but there was no obstruction of the portal vein. If there had been any disturbance it would have been due to the passage of the venous blood through the liver.

ILLUSTRATIONS.

FIG. 1.—Diagram of conditions found in case described.

- A. Obliterated trunk of inferior vena cava.
- B. Obliterated ductus venosus.
- C. Obliterated umbilical vein.
- D. Junction of lower part of inferior vena cava (F) with (E) portal vein. GG. Enlarged right azygos vein opening into vena cava at I just below renal veins and above the termination of the thrombus. (H).

FIG. 2.—Schematic diagram of development of body veins. Probably all processes shown here do not occur simultaneously. The cross hatching indicates the channels which normally persist.

A. Path of formation of vena cava inferior in the hepatic plexus. This is evidently the point at which obliteration took place in this case.

D. Shows the way in which connection might persist between the vena cava and the portal E. F the upper extra hepatic part of the vena cava forming connections with the subcardinal plexus.

I. The persistent connection of the postcardinal trunk with the plexus which goes to form the lower vena cava. This constitutes in Fig. 1 the connection I of the right azygos with the vena cava. J the supra cardinal plexus which finally becomes the lower trunk of the cava liberating the ureter.

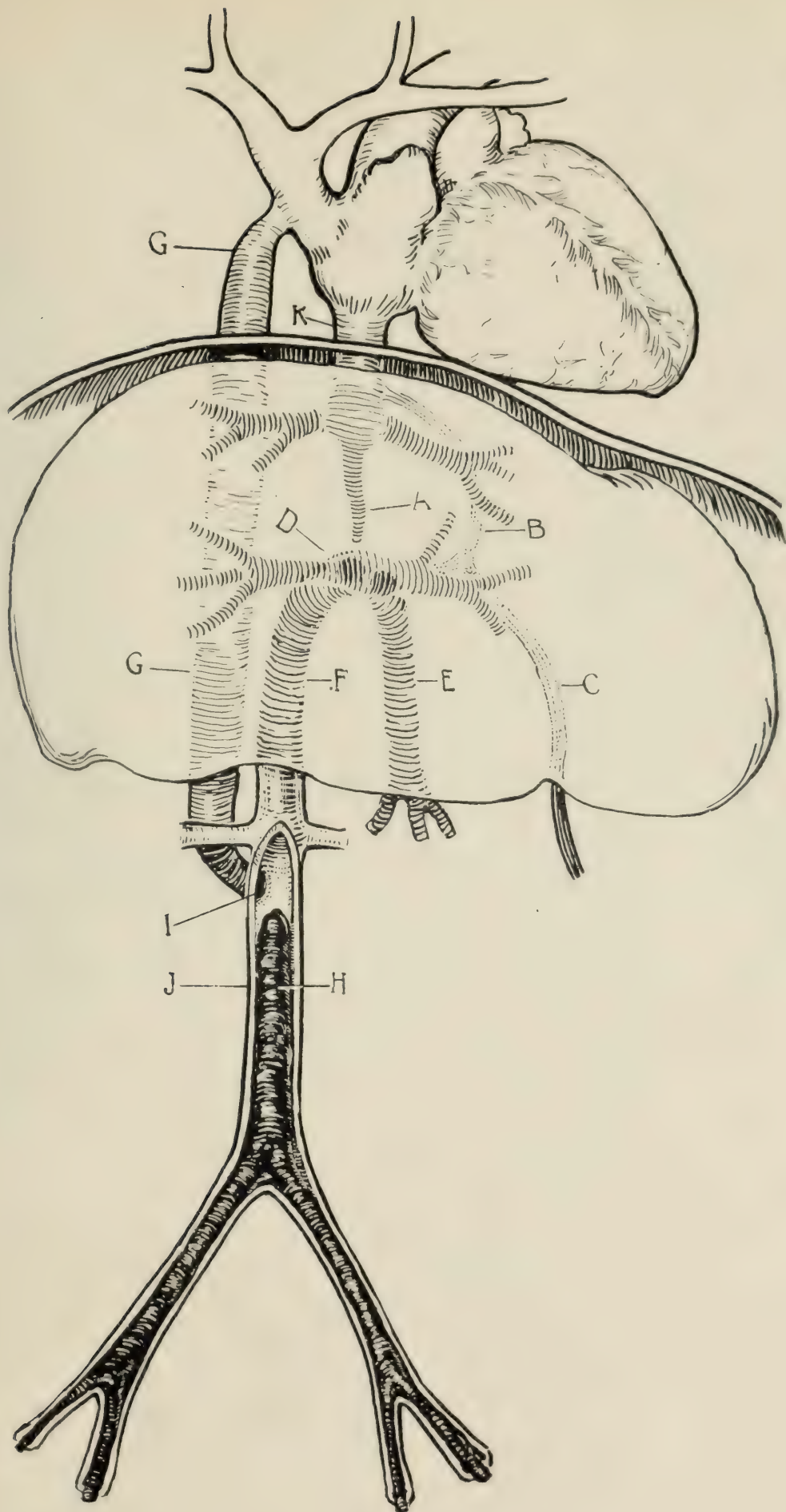


FIG. I.

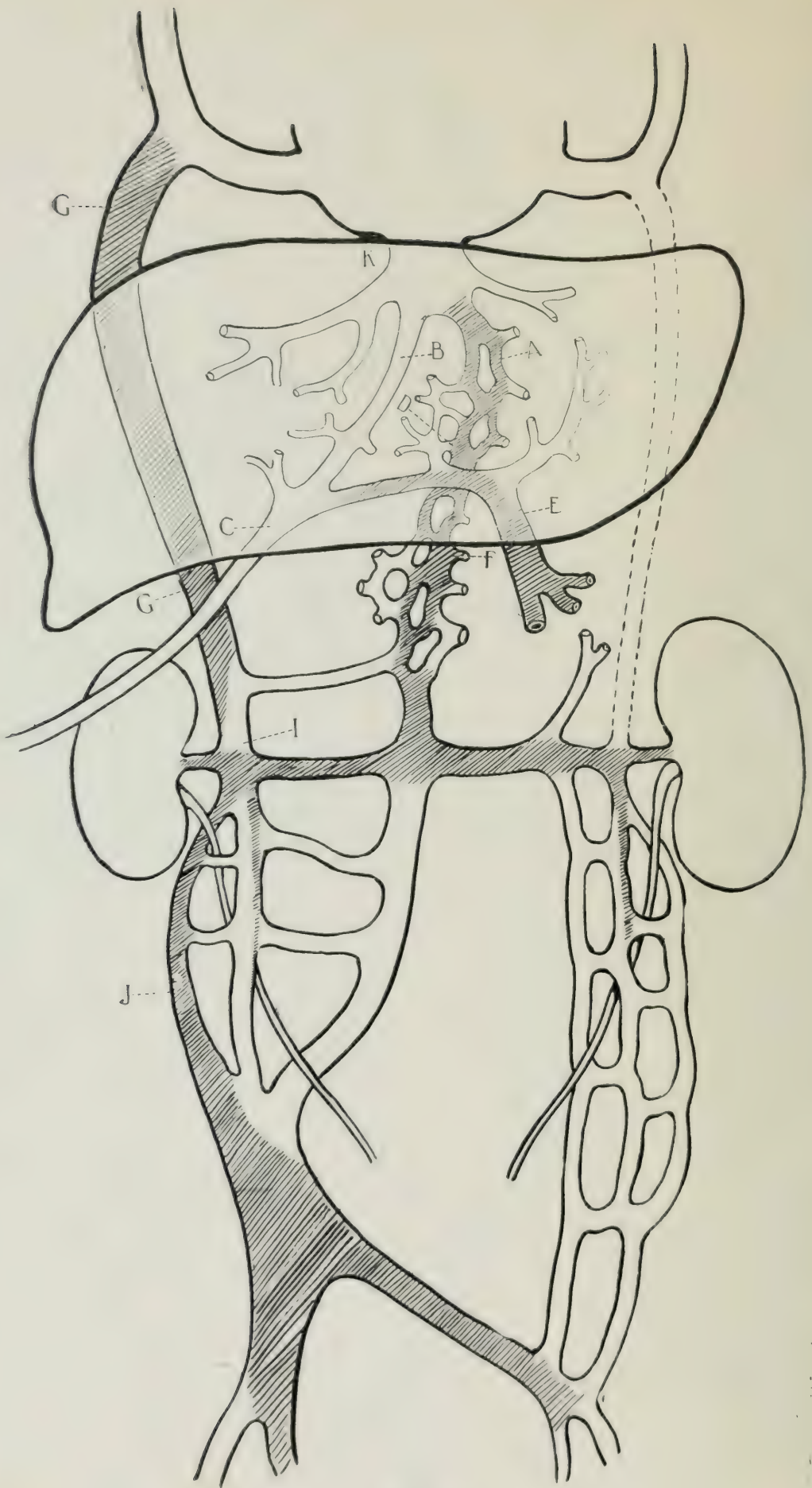


FIG. II

MUCOCELE OF THE APPENDIX.

O. V. HUFFMAN, M.D.

False diverticulum, that is hernia of the mucosa and submucosa through the muscular wall, has been described as occurring in the appendix by many authors. In addition to the simple hernial sac there occurs frequently a more complicated condition, a condition where the sac is not completed by epithelium, and mucus is held in a mesh of connective tissue. This condition was regarded as colloid cancer by Virchow and Rokitansky, but later observations have revealed its benign nature. In fact most of these tumors have been discovered quite by chance either during an intra-abdominal operation or at autopsy. These herniæ or mucocèles are generally regarded as having had their origin in a remote inflammatory process. It is because the specimen here presents several points of interest in regard to its etiology, that I am reporting it.

Case: The appendix was removed by Dr. Cragin, at Sloane Hospital. The patient had been observed previously by Dr. Levin. The patient is a woman, married, about thirty years of age. Four months ago she had an attack of pain in the right iliac region, accompanied by some fever, and four months previous to that attack she had had a similar one. Dr. Levin reports that there were marked symptoms of local peritonitis. The appendix was removed during an intra-abdominal operation for retroversion of the uterus. A moderate sized lipoma was also removed from the buttock.

Gross Description: The appendix was about 5 cm. in length. Near the distal end, it was surrounded by a mass composed of small cysts, filled with clear gelatinous contents. On opening the lumen of the appendix by a longitudinal incision, it was observed that just to one side of the lumen, before reaching the cyst, there is a dense fibrous mass, about 1 cm. in diameter. This mass causes no occlusion of the lumen. The lumen becomes lost in the cystic mass. The cystic mass is about 2x3x3 cm.; it is divided into numerous small compartments. Distal to where this cystic mass

communicates with the lumen of the appendix, the appendix is found in an apparently normal condition.

Microscopical Description: Section 1; Taken from the portion of the appendix proximal to the tumor; this shows normal mucosa and muscularis.

Section 2; Taken from the portion of the appendix with the fibrous nodule, just proximal to the cystic tumor; This shows normal mucosa, and to one side a large mass composed of hyaline and cellular connective tissue beneath the muscular coat.

Sections 3 and 4; Taken from the cystic tumor. Here one finds a remnant of normal mucosa, which no longer forms a lumen but is present simply as a tape, between which and the peritoneum there is a mesh of connective tissue filled with mucus. In these transverse sections the epithelium of the normal mucosa becomes gradually reduced to a layer of very low and small cells, which can be traced no further into the cystic mass.

Section 5; Taken from that portion of the appendix distal to the tumor. Here one observes a section through a normal appendix, and a portion of the overlying, so-called hernial, protrusion of mucus membrane belonging to the cyst.

If tumors such as these are to be regarded as a result of inflammation and weakening of the walls of the appendix, thus permitting a protrusion of the mucosa, there should be some explanation in this case as to the normal condition of the distal portion of the appendix, and some explanation for the gradual transition of normal mucosa into the cystic tumor. These tumors are explained by most authors as being caused by a damming back of mucus against a weakened portion, both the obstruction and the weakening being a result of inflammation. In this way, Edel explained a similar case where, too, there was a mass of scar tissue just proximal to the diverticulum. To offset this case, however, is one reported by Fischer, where the constriction and obliteration of the mucosa were distal to the diverticulum. It is also of interest to note that in Fischer's case, where the muscularis was missing, the connective tissue instead of bulging outward, was drawn towards the lumen of the appendix. I mention this,

because it suggests that it would require more than a sub-peritoneal or intra-muscular inflammation to cause a hernial protrusion; that the strong layer of connective tissue in the submucosa would have to be destroyed. An ulceration destroying the wall of the appendix and producing a tumor such as the one shown here would be unlike the result following ulceration in any other portion of the alimentary tract.

As to the possible congenital origin of these tumors, it is to be mentioned that Hedinger found an appendix with diverticula in a newly born infant, and that he sought to explain the origin of these tumors generally as of such origin, but that Winkler, who has made an extensive study of the diseases of the appendix, is not able to find any further evidence for such an explanation. Still there remains the fact that the majority of the tumors, such as the one reported here, have been found accidentally, either at autopsy or during an intra-abdominal operation for some other purpose.

To summarize then, this specimen is of interest, because of the normal condition of the appendix both above and beyond the site of the tumor, the transitional portion of the epithelium, the clinical history of appendicitis, and the inadequacy of the obstruction theory for the production of such a condition.

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Discussion.

DR. MOSCHCOWITZ: Some time ago we had a case of mucocoele of the appendix at the Beth Israel Hospital. The appendix was removed during the course of an abdominal operation. At the tip was found a small cystic mass the size of a millet seed. On section this showed a large cavity filled up with connective tissue, which went out through a small hernia in the muscular coat; there a hematocele was formed and I gathered the impression that there had been distension of the muscular coat.

DR. WOOD: These cases of mucocoele are also very interesting from an aspect entirely different from that brought out; that is, the differential diagnosis between this lesion and gelatinous carcinoma. As every one knows, there are cases of gelatinous carcinoma arising in the intestine in which the entire mass is composed of a few strands of connective tissue lying in a clear jelly-like substance, and none of the characteristic signet-ring cells can be demonstrated. Keeping this fact in mind it becomes difficult to say without thorough examination of a specimen of mucocoele that no malignant growth is present. The most important differential point is the fact that in the mucocoele the gelatinous substance penetrates between the muscle tissue and the connective tissue strands, leaving them unaltered; while in the gelatinous carcinomata the tissues are separated by the tumor which forms more or less roughly spherical alveoli, thus compressing and distorting the normal structures through which it grows. In the specimen of mucocoele of the appendix which we had some time ago at St. Luke's, a prolonged examination of many sections was necessary before this point could be cleared up, as at first I was quite certain that the lesion was of a malignant nature.

DR. EWING: Dr. Huffman has just presented a case of mucocoele of the appendix. Dr. Moschcowitz has mentioned another. Dr. Wood a third. A fourth is being presented before the Surgical Society to-night, and we have a fifth at Cornell, and yet the etiological factors are but vaguely understood. Would not

it be well for some one to gather together all of these cases and investigate the modes of origin of the process?

DR. HUFFMANN: Many cases have been reported but there is great confusion in the literature concerning them. Some authors report them as tumors, others as retention cysts.

CONGENITAL CYSTIC MALFORMATION OF THE LUNG.

ALWIN M. PAPPENHEIMER, M.D.

The case presented illustrates a rather unusual type of congenital malformation of the lung, examples of which are found in the literature under such divergent terms as Congenital Cystic Malformation, Fetal Bronchiectasis Polycystic Degeneration of the Lung, Papillary Bronchial Adenomata, etc. The discordant nomenclature indicates the different views which have been held as to the genesis of the condition.

The case is from the service of Dr. Studdiford at the Nursery and Child's Hospital, and I am indebted to him for permission to report the clinical findings. The mother of the infant was brought to the hospital in the seventh month of her pregnancy, suffering from a severe pyelitis, with uremic symptoms. She is still severely ill, but apparently recovering. Soon after her admission, she was spontaneously delivered of a premature male child, which lived for about three hours under artificial respiration. During this time, it was only moderately cyanosed, and made some spontaneous efforts at breathing.

There were four previous children, all living, and one spontaneous miscarriage, two years ago. No direct or indirect history of syphilis could be obtained from the parents, but a Wassermann reaction taken after the child was born, proved to be strongly positive.

The autopsy was performed forty-two hours after death. The body was that of a 42 cm. obviously premature male infant. There was marked lividity of the head and shoulders. Cord still moist. Eyes, ears, nose and mouth normal. Skin shows no lesions. No external anomalies. Umbilical and hypogastric vessels contain fluid blood.

On removing the sternum, a large part of the anterior surface is seen to be occupied by the enlarged upper lobe of the right lung, which extends slightly beyond the median line, from the second rib to the liver. (Fig. 1.) The heart is displaced to the left, the apex lying beneath the fifth rib, $3\frac{1}{2}$ cm. from the median line. The thymus is also pushed over to the left, extending to the third interspace. The left lung appears relatively small and collapsed, lying in the posterior part of the thorax.

The right upper lobe is extremely voluminous, 7 cm. from apex to lower border and about 6 cm. in width. The surface is smooth, showing none of the normal lobular markings; it is reddish pink in color, rather translucent and elastic. There are scattered small hemorrhagic blotches beneath the pleura.

On the septal surface, especially near the posterior portion, there are numerous rounded translucent elevations, up to 1 cm. in diameter, through which clear fluid can be seen. These are separated by more opaque whitish septa.

The apex of the lobe is occupied by a cap of normal appearing lung tissue, which overhangs slightly the rest of the lobe behind and is sharply demarcated from it.

The lower and middle lobes are relatively small, darker in color and evidently poorly aerated. The same is true of the entire left lung, which shows no external malformations.

After hardening, the specimen was injected through the trachea, under moderate pressure, with a solution of Berlin blue in gelatin. All the lobes were readily injected, although the diffusion of the mass was somewhat irregular, owing to the preliminary fixation. In the right upper lobe, however, the injection is limited absolutely to the cap of normal appearing lung tissue which constitutes the upper pole. A section made through the

upper lobe shows a sharp and very distinct demarcation between the upper injected portion and the lower uninjected part.

A dissection of the main bronchus shows that there is a branch of small caliber, derived from the right main primary bronchus, distributed to the cap of normal lung tissue at the apex of the lobe. But even a careful search fails to show any branch running to the lower spongy portion, into which a bristle can be passed. The bronchi to the middle and lower lobes and to the left lung, are normal. Nor is there any abnormality found in the distribution of the pulmonary arteries and veins.

A section through the upper lobe shows a sharp division into two portions—an upper injected part resembling normal lung tissue but partially atelectatic; and a larger lower portion, in which the tissue is decidedly paler and spongy in structure, being composed entirely of smaller and larger cystic spaces separated by rather stout septa or trabeculae. These cystic spaces reach the size of almost 1 cm., the largest ones being situated near the septal surface. They are approximately circular in outline. In the depths of the tissue are several rather thick tubular structures; whether these are vascular or bronchial in nature cannot be determined from the gross appearance. No tubular structures are seen near the hilus.

Section through the remaining lobes of the right lung and through the left lung show nothing abnormal. The lung tissue is poorly aerated and hyperæmic; the injection mass has penetrated somewhat unevenly, but is present in all the lobes.

The *heart* is normal in size and conformation. There are no valvular lesions or anomalies. The foramen ovale is somewhat more widely patent than one would expect at this age, but is well formed. The ductus cannot be probed, and is almost, if not entirely closed.

Liver is normal in size. There are several sub-capsular hemorrhages on the anterior surface. The surface of the cut section is very oedematous, of a uniform greyish pink color, without lobular markings.

The *spleen, kidneys, adrenals and bladder* show no note-

worthy changes. The *thyroid* is large, the lateral lobes extending to the face of the pharynx. Behind the R. lobe, there is an oval, pinkish body, 2 cm. in length, resembling thymus in texture, and proving to be such on microscopic examination. The *parathyroids* were normal, three being found.

The microscopic findings in the different organs, in so far as they have a possible bearing on the case, are as follows: The liver contains very numerous blood-forming islands. There is no increase in connective tissue. The *spleen* shows an engorgement of the sinuses; there are many nucleated red cells, but comparatively few pulp cells. The follicles are small, irregular and poorly formed. The *pancreas* shows the acini separated in places by a loose embryonic connective tissue in which are found small areas containing very numerous lymphoid cells and granular eosinophiles. These areas are especially seen in the neighborhood of the larger pancreatic ducts and arteries. A few solid nests of cells, representing poorly formed islands, are found. The *testis* contains an unusual number of capillaries, which are engorged with blood. There has been some extravasation between the tubules, and there are a few clumps of yellow pigment. The *adrenal* has a very broad cortex, in which the narrow glomerular zone exhibits the formation of distinct lumina; the capillaries of the reticular zone are congested.

Sections of thymus, adrenal, liver and kidneys examined for *spirochaeta pallida* by the Levaditi method, were negative.

Lungs: Sections through the spongy portion of the right upper lobe show a great number of irregular spaces, up to 1 or 2 mm. in size. The smaller ones are lined with flattened cells, are surrounded by well-filled capillaries, and are separated from each other by more or less stout septa. They resemble normal alveoli in all respects. These alveolar spaces are empty, apparently containing none of the coagulated granular material which is found in the larger cystic spaces. In the thicker septa are numerous connective tissue cells with pale oval nuclei and comparatively few collagenous fibrils. The elastic framework is well developed. In eosin-methylene blue preparations, there are found quite a

number of normoblasts, some of which are extra-vascular, and a few granular eosinophiles.

The larger cysts are lined by high cuboidal or columnar epithelium, which is for the most part distinctly ciliated. The walls are not smooth, but the mucosa is thrown up into corrugated folds, which in places are extremely redundant, forming papillary projections into the lumen. Mitoses are not found, probably because of the lateness of the autopsy, since the appearances certainly suggest active proliferation.

In the lumina of the cyst-like spaces, is a shreddy or granular material, evidently not mucinous in character, and consisting in part of cast-off cilia. There are also here and there a few desquamated cells, which are for the most part round and apparently derived from the alveolar, rather than the ciliated cubical epithelium. The amount of demonstrable cyst contents is extremely small, the majority of the spaces appearing entirely empty.

From the primary cavities, tubular gland-like prolongations are given off, and may be traced in serial sections for a considerable distance. Often there is a slight constriction at the neck of the tubule, and on cross section, the small evaginations closely resemble tubular glands. Goblet cells are never found, the tubular outgrowths, like the larger spaces, being lined with ciliated epithelium. They may bifurcate before ending blindly.

The epithelium of the dilated bronchioles, for such they are, rests almost directly upon a membrane of elastic tissue, composed of three or four laminae of stout fibers. The areolar tissue separating the cysts from one another, also contains a loose feltwork of elastic fibers. In the wall of many of the cyst-like spaces are thin bundles of smooth muscle fibers, circumferentially disposed; about most of the spaces, however, they are absent.

Some of the spaces have definitely the character of bronchi. Their wall contains small crescentic islands of cartilage, and rather stout bundles of smooth muscle fibers which, however, never completely encircle the bronchus, but are arranged in discontinuous bundles. The epithelium clothing the bronchus is of a character similar to that in the cyst-like spaces described, though

somewhat higher, and in places heaped up into several layers. It is likewise definitely ciliated.

Of importance for the correct anatomical interpretation of the anomaly, is the relation of the cyst-like spaces to the bronchi, on the one hand, and to the alveoli on the other. This could be easily determined in serial sections, and it was found that the dilated spaces were not closed cysts, but in direct communication with both the larger bronchi and with the alveoli. As the bronchus passes into the dilated portion, it frequently becomes narrowed by the projection of valve-like folds of epithelium. It then widens out into the irregular cavities described, and from the terminal portions of these, corresponding to the normal infundibula, the alveolar spaces are budded off. But it is of interest to find that the transition between ciliated and flattened alveolar epithelium is not a regular and gradual one, but that different portions of the same infundibular enlargement are lined in some portions, by epithelium of the cuboidal ciliated type, in others, by flattened alveolar cells.

The blood vessels, both in the normal and the spongy lung tissue show no departure from the normal structure.

Since the case described by Meyer¹ in 1858, similar cases have been reported from time to time by Grawitz,² Balzer and Grandhomme,³ Couvelaire,⁴ Dionisi,⁵ Arnheim,⁶ Pepere,⁷ Stoerk,⁸ Sandoz,⁹ Buchmann¹⁰ and others. The cases fall into two groups—those occurring in premature or new-born infants, in which the condition is apparently incompatible with life; and the cases found in later life and interpreted for various reasons as congenital. These instances of fetal bronchiectasis found in the lungs of older individuals, are often obscured in their interpretation by the presence of secondary inflammatory changes, but the complete absence of pigment in the affected area is usually taken to indicate their congenital origin.

As regards the cystic malformation in the new-born, two types may be distinguished, between which all transitions have been described. The first is illustrated by a case reported by Wechsberg.¹¹ Here there was found a tumor in the left pleural

sac attached merely by a fibro-vascular pedicle to the pleural covering of the oesophagus. It contained numerous cysts filled with clear fluid and showed microscopically the same structure as the case shown here. In this case, there was, of course, no communication with a bronchus. Wechsberg believes that the tumor arose from an accessory lung Anlage, arising separately from the oesophagus, with secondary obliteration of the connecting canal. Klebs had previously described such a rudimentary lung given off below the diaphragm.

In contrast to this case in which the cystic lung tissue is entirely separated from the normal lung, are the cases such as those of Arnheim⁶ and Pepere,⁷ in which the cystic changes affect an entire lung, or even both lungs to a greater or lesser degree. In the majority of cases, the cystic change has been restricted to a single lobe or to a portion of it, as in the case presented.

A communication between the dilated spaces and the larger bronchi has been established in certain cases by inflation; in many of the cases, however, there is a definite record that the cysts contain fluid and are not connected with the bronchi. Thus Couvelaire⁴ has described a specimen in a new-born child in which the tissue at the hilus of the affected lobe contained not a single bronchus.

The various views regarding the genesis of the condition, may be grouped under three headings:

I. The condition is to be looked upon as simple arrest of development at a period more or less advanced. This theory explains the embryonic structure of the bronchioles and infundibular spaces and the absence of completely differentiated bronchi, but does not give a reason for the dilatations or cyst formations. Moreover, in those cases in which there is an absence of the larger bronchi, it is necessary to assume that these have undergone a regression or secondary obliteration. We have an analogy for such a process in the normal obliteration of canals derived from the fore-gut, as in the case of the pharygo-hypophyseal duct, the thyro-glossal duct, and the canals in the cervical portion of the thymus. It does not seem strained to assume that a similar pro-

cess may occur abnormally in the developing lung bud, but the actual demonstration of such a secondary obliteration has not been given.

II. The entire process is the result of a fetal inflammation, with inflammatory stenosis or atresia of the bronchi, and bronchiectatic dilation of the distal portions from stagnation of the secretions. This explanation must be discarded for those cases in which a communication with the bronchus persists. It is further objectionable in so far as no histological evidence pointing to the occurrence of an inflammatory process has been brought forward. The only exception is the case of Balzer and Grandhomme,³ in which the unaffected lung showed definite syphilitic changes, and a thickening about the vessels and bronchioles is described in the cystic lobe. But here, as Couvelaire⁴ and Humbert¹² have pointed out, there may have been simply a coincidence, the anomaly occurring in a syphilitic lung. None of the other recorded cases in young infants have shown inflammatory changes and where such are present in later life, they are doubtless secondary. Furthermore, the formation of bronchiectases by simple stagnation of secretion, is questionable, and the irregular appearance of the dilated spaces with their villous or reduplicated lining, does not in the least suggest such an origin.

Nevertheless, the occasional association of syphilis with this anomaly, as in the case of Balzer and Grandhomme,³ in the two cases reported by Sandoz,⁹ and possibly in the present case, is of interest; and it is possible that a more careful inquiry would show that in the production of this as in other anomalies depending essentially upon an inhibition of development, syphilis plays a dominant role.

III. The third hypothesis is that maintained by Stoerk,⁸ which interprets the condition as a tumor growth. Stoerk has applied the term "cystic fetal bronchial adenoma" to the neoplastic process, and believes that it is possible to differentiate cases of this type from cases of fetal bronchiectasis due to inflammatory stenosis. His principle argument for considering the condition as a neoplasm is that the dilatation of the bronchi is accompanied

often by tubular outgrowths into the septa. It seems to the writer that little is gained by applying the term tumor to an anomaly of this sort. That the failure of complete differentiation is accompanied by a normal or even excessive growth, is probably true, and to this excessive growth, rather than to a passive distension by secondary products, is attributed the formation of the dilated spaces and the increased size of the affected lung or lobe. Whether one shall apply to such a simple overgrowth of undifferentiated tissue the term neoplasm, is of no particular consequence, since such a view adds nothing to our knowledge of the causation of the condition.

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ILLUSTRATIONS.

FIG. 1.—Heart and Lungs: natural size. Only the malformed upper lobe of the right lung is seen from the anterior aspect.

FIG. 2.—Section through right upper lobe. Dilated bronchioles lined with ciliated epithelium; in the septa, normal alveolar tissue. x 80.

FIG. 3.—Section through dilated bronchus and adjacent tissue. B.—Bronchus; C.—Cartilage; M.—Smooth muscle fibers; Br.—Dilated bronchioles. x 80.

Discussion.

DR. MOSCHCOWITZ asked whether in his survey of the literature, Dr. Pappenheimer had found that congenital cystic lung was associated with congenital cystic kidney. Some years ago in a study of congenital cystic liver he found that various authors frequently mentioned the association between congenital cystic degeneration of the lung, liver and kidney. Dr. Moschcowitz had come to the conclusion that congenital cystic liver was due to a malformation; and that the lesion was due to a dilatation of aberrant intra-acinar bile ducts. Fully developed intra-acinar bile ducts were found in an apparently normal liver, microscopically, in a foetus that had cystic kidneys and various congenital malformations such as supernumerary digits, encephalocele and spina bifida. In cystic livers these fully developed ducts can be demonstrated within the lobule of the liver. For these reasons, Dr. Moschcowitz has concluded that cystic liver was a result of a malformation, and, inasmuch as cystic lung was associated with cystic liver, that congenital cystic lungs were also the result of a malformation. In other words, that the spaces which made up the bulk of the lesion were primitive or embryonal bronchi which had failed in their further development.

DR. STEWART: We are always looking for the developmental mechanical factor in the formation of bronchiectases. What is the nature of this factor in this case?

DR. PAPPENHEIMER, in answer to Dr. Moschcowitz, said that he had only approached the literature from the lung side. There were no cystic kidneys in his case, nor had he found any reported in the literature in connection with cystic lungs. In answer to Dr. Stewart's question, he admitted that the arrest in development did not in itself account for the dilatation, but it seemed to him that one had to assume an excessive growth in association with the arrested differentiation.

DR. NORRIS: What was the character of the epithelium lining the cyst?

DR. PAPPENHEIMER: The spaces are lined with a columnar or cuboidal ciliated epithelium.



FIG. I



FIG. II



FIG. III.

THE TRANSPLANTABILITY OF MALIGNANT TUMORS TO THE EMBRYO OF A FOREIGN SPECIES.

JAMES B. MURPHY, M. D.

The phenomenon of tissue specificity, that is, the failure of transplantation of tissues of one species into the body of another, has been the subject of much speculation among experimenters, with as yet no adequate explanation. It has been of particular interest to cancer investigators, as it represents the great barrier that prevents the transfer of human tumors to lower animals. Wider experimentation has shown that this line between species is more closely drawn than was suspected, and it is even found to divide the varieties of the same species. Well-known examples of this are the failures in transplantation of the tumors of the white mouse to the brown or grey mouse, or tumors of the white rat to any other than white rats. A more recent example is that of the Rous chicken tumor,¹ which in its first transfer grew only in blood-related animals, and later only in animals of the same breed as the original fowl.

Remarkable as this phenomenon is, it has not been the subject of as extensive research as its importance would warrant. There has been a general impression that one of the immunity processes is responsible for this reaction, but no very definite evidence is at hand. Ehrlich includes an explanation of it in his ingenious hypothesis for tumor immunity, the so-called athrepsia theory.² This is briefly that the cells of an organism possess a certain specific binding power for the circulating food particles. When a cancer graft is introduced into an animal, if its attraction and binding power for the food particles is greater than that of the host cells, it grows at the expense of the other tissues. If, however, the binding power of the cancer is lower than that of the host tissue, the cancer cells fail to grow and die from lack of nourishment. Animals showing this latter condition are called naturally immune. The artificial immunity to inoculable cancer, produced by a previous introduction of living cells into the ani-

mals, is accounted for by the presumption that these cells bind all the available food, leaving none for the cancer to utilize in its growth. The failure of growth of a tissue introduced in a foreign species, as is naturally deduced from the foregoing explanation, comes from the inability of the cells to combine with and utilize the alien food particles. The temporary survival of cells in a foreign species host, Ehrlich claims, is adequately accounted for by the native food carried with the graft from the original species. This latter phase of the hypothesis is the one of interest in the present research.

We reported last year the successful inoculation of a fowl sarcoma into the developing chick embryo.³ In the course of this study the interesting observation was made that the tumor grew equally well in the developing pigeon or duck embryo, whereas in the adult of these species it quickly died and was absorbed. This finding suggested two possibilities: either the embryo provides a food substance utilizable by the tissues, which is lacking in the adult, or else the embryo lacks a defensive mechanism possessed by the adult. The results I wish to report to-night were obtained with tissues from more distantly related species, namely, mammalian tissue inoculated into embryos of the common domestic fowl.⁴

The technique is very simple. A small rectangular window is cut in the shell with a sharp instrument. The shell membrane is broken and pulled back with sterile forceps, exposing the embryo and its membrane. The material used is hashed finely and injected by means of a hypodermic needle into the desired location. After the inoculation the bit of shell is replaced and sealed with paraffin. By this method I inoculated a fine hash of the Jensen rat sarcoma*⁵ into the outer membrane (fused allantois and chorion) of five to seven days embryos. These were then incubated from ten to twelve days, that is, to within two days of hatching. When the shell was removed and the membrane cut

*This tumor was selected for the work as it is the generally known and one of the most widely worked with of the transplantable tumors.

¹*Jour. Exper. Med.*, 1910, xii, 696.

and turned back, in a high percentage of instances the egg was found to have, at the point of inoculation, a rounded, globular mass, suspended from the membrane by a broad, flat pedicle. The masses varied in size from 0.2 to over 2 cm. in diameter. The consistency was that of firm jelly, varying in color from pinkish-grey to red. The surface was smooth and glistening, with numerous large dilated vessels coursing over it, and smaller vessels were visible in the semi-translucent substance of the tumor itself. On section the masses were found to be solid and composed throughout of this pinkish-grey, somewhat translucent tissue, with small areas of hemorrhage in some cases. The tissue was quite moist and friable.

Moreover, it was found easy to re-inoculate these embryonic grown tumors into a second series of embryos. The tumors from this second generation are of the same types as those of the first, and grow with equal rapidity. These in turn can be transferred to a third and fourth lot. This rat tissue has grown for as long as forty-six consecutive days in the foreign species embryo.

Naturally the change and possible adaptation of this tissue to the new conditions has considerable interest. As far as the morphology of the growth and of the cell is concerned, there is little or no change. The tissue when returned to the rat after the long sojourn in the foreign host gives rise to a tumor that grows as rapidly as when the tissue is transferred from another rat. On the other hand, the tissue acts differently when placed in an adult chicken. Tissue taken directly from a rat will survive for three days in the adult chicken and for about the same length of time in the newly hatched chick. On the other hand, when this same rat tissue is grown for a period in the chick embryo and then placed in the adult, no living cells can be found after twenty-four hours. This condition is also noted in the newly hatched chick. In some cases the inoculations were made a very short time after the animals emerged from the shell and they were kept in the incubator without food or water for the first twenty-four hours so as to change the conditions as little as possible. Instead of adapting the rat cell to a new host we have made it more susceptible to defensive forces.

A variety of other tissues have been grown with equal success to that of the Jensen sarcoma, namely: chick embryonic tissue, rat embryonic tissue, a sarcoma, a carcinoma, a chondroma of the mouse and the Flexner-Jobling adenocarcinoma of the rat.

Conclusions: The experiments show conclusively that mammalian tumor tissue can live and grow actively in the chick embryo, although in the adult it dies quickly and is absorbed. By transfer from embryo to embryo the mammalian tissue can be kept growing for as long as forty-six days and probably indefinitely. This proves beyond doubt the ability of the mammalian cell to utilize the food supplied by the avian embryo. There seems little doubt, from a study of the fate of the grafts of this same tissue in the young chicken and in the adult, that they possess a defensive mechanism which causes the death of the tumor cell, rather than that the grafts die from lack of nourishment. The changes that take place in the rat cells after their long dependence on the foreign species host are certainly slight. Whether a still longer period of dependence will bring about an adaptation of these which will render them capable of growth in the adult remains to be seen, but present results offer little encouragement in this direction.

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Discussion.

DR. LAMBERT: In our tissue culture studies, Dr. Hanes and I found that while rat sarcoma cells may proliferate for a month or more in certain foreign plasmas (guinea-pig plasma, for example), the duration of growth in chick or pigeon plasma is, as a rule, only three to five days.

In view of Dr. Murphy's results, it would be interesting to see if there is any difference in the duration or character of the

growth of rat tissues in embryonic chick plasma and in plasma obtained from chicks after hatching.

DR. ROUS: I wish, with Dr. Murphy's permission, to add an interesting feature noted in his experiments. The rat tumor grows in the chick embryo at a temperature of 41°C , whereas in the rat it grows at 37.6°C . This fact would tend to show that the regression of tumors during febrile processes, cannot be due directly to the increased body heat, as is so frequently assumed.

DR. LEVIN: When a tumor is placed in the egg is it always brought in direct contact with the embryo or its membranes, or does it frequently float freely in the yolk of the egg? It is possible that in either instance the tumor cells obtain their nourishment from the yolk, and then the inoculations of the tumor into the egg are comparable to the experiments of Dr. Lambert, where rat tissue grew in vitro in chick plasma. When the yolk disappears and the only nourishment obtainable by the tumor cells is the specialised food of the chick embryo, then the growth of the rat tumor ceases.

DR. MACCALLUM: Do not these tumors acquire a vascular supply?

DR. EWING: What is the morphology of the cells of these tumors and do they differ from those of ordinary rat tumors?

DR. MURPHY: There is no variation in the morphology of the cells: even after forty-six days' growth in the chick embryo the cells are distinctly those of a rat tumor. The structure is not so compact. In answer to Dr. Levin I would say that the tumor grows only when brought in direct contact with the chick embryo or the embryonic membranes. It receives a tremendous vascular supply, and a certain amount of stroma from the host.

A CASE OF ACUTE MILIARY TUBERCULOSIS.

A. B. EISENBREY, M.D.

Clinical History: The patient, aged sixteen months, was admitted to St. Luke's Hospital in July, 1912. The symptoms at that time were pain in the abdomen, diarrhoea, and jaundice. No family history of tuberculosis was obtainable. The patient was running a moderate regular fever. No bile was found in the urine. A diagnosis of tuberculous peritonitis was made, but at operation the peritoneum was found not to be involved, though the retroperitoneal glands were markedly enlarged. None of these were removed, however. After one month the patient left the hospital, his general condition being somewhat improved; but on November 4, he was re-admitted in a moribund condition.

Autopsy findings: There was a generalized milary tuberculosis, notable because of the enormous numbers of tubercle bacilli found in sections of the liver, spleen, kidneys, and lungs. The peritoneum was thickly studded with tubercles, and in the ileum there were seventeen large ulcers easily recognizable from the peritoneal side, in several places causing adhesions between adjacent loops of intestine; but no perforation had occurred. The entire group of retroperitoneal glands was matted together in a mass about 12 cm. in diameter. The glands were greatly enlarged and caseated. In addition to the milary involvement the left lung showed an ulcerative process and cavity formation at the apex. The cavity contained fresh blood clots and there was erosion of the vessels passing across it. Since the lungs were not found to be involved during the patient's stay in the hospital in July, it is reasonable to believe that the tuberculosis was primary in the peritoneal glands, that the lung development occurred later, and that the cavity in the lung acted as the distributing point for the milary involvement.

The liver was markedly enlarged and appeared fatty. The gall-bladder was distended and its wall thickened. Firm pressure failed to force bile through the duct and it was found that two enlarged glands compressed the duct between them. On dissect-

ing away one of the glands the bile was readily expressed. The patient was markedly jaundiced, but microscopical examination failed to show a dilatation of the bile capillaries in the liver.

Discussion.

DR. WOOD: This case is of considerable interest as showing the very short time in which a diffuse growth of miliary tubercles can take place throughout the body. The fact that no tubercles were seen at the time of the laparatomy some months before the child's death is sufficient proof that there was no generalized miliary tuberculosis at that time, so that the whole process must have been quite a recent one. Despite the lack of dilatation of the small bile ducts I still think that the jaundice was probably an obstructive one. A very moderate degree of pressure on the common duct, such as was caused by the tuberculous lymph node demonstrated, will give rise to moderate jaundice without complete obstruction of the flow and without great dilatation of the capillaries, especially if the obstruction has existed for only a short time. The sections of the liver are very interesting. I have never seen so many tubercle bacilli in one section. It looks like a sputum concentrate after the use of antiformin, the entire field being covered with organisms.

DR. NORRIS called attention to the translucent foci resembling miliary tubercles, on the edges of the tricuspid valves, which Dr. Eisenbrey had shown to him before the demonstration.

DR. MACCALLUM: Was the actual portal of entry determined?

DR. EISENBREY: The portal of entry was the cavity in the lung.

CALCIFIC AND OSTEOGENIC CHANGE OF THE LEFT AURICLE IN A CASE OF AURICULAR FIBRILLATION.

B. S. OPPENHEIMER, M.D.

The following case is reported on account of the increasing interest shown of late by general pathologists and pathological chemists in calcification and ossification and because of the rarity of these two processes in the human heart.

The heart was obtained from a patient, a violinist by occupation, forty-four years of age. He had a mitral stenosis and associated with the stenosis that common clinical condition, auricular fibrillation.

The electrocardiogram taken, through the courtesy of Dr. Horatio Williams, about a month before the patient died, showed not only that there was auricular fibrillation but also that the right ventricle of the heart was relatively more hypertrophied than the left. There have not been many instances in which it has been possible actually to confirm such an electrocardiographic record indicating hypertrophy of the right ventricle by a post-mortem finding. This particular heart showed as great a relative right-sided hypertrophy as any which we have had an opportunity of examining. The sino-auricular node in this heart has (as you see), been cut out from the right auricle in the endeavor to locate, if possible, the lesion which caused the auricular fibrillation.

The left auricle presents an extensive calcification, so that the whole of it except the auricular appendix and the interauricular septum, feels like a bony plate; in fact, microscopic examination shows that a portion of this plate is indeed undergoing an osteogenic process. So far as I am aware, though new formation of bone has been found in many different organs in the body, yet, with the exception of the valves, it has only once been reported in the human heart. Poscharissky¹ found bone in the annulus fibrosis of the left ventricle.

Only three small blocks of tissue from the hard left auricular

wall were sectioned and in one of these we encountered an area undergoing ossification. This area presents both calcified and non-calcified osteoid tissue. The hard plate in the left auricular wall consists of hyaline degenerated connective tissue, much of which is calcified.

The lime deposit is distributed throughout the inner coat of the left auricular chamber, and the inner coat only, leaving the striated musculature untouched. For the most part it is in the shape of scattered granules and of plaques (diffusely impregnated tissue) bordered by coarse granules; but also, though more rarely, it is in the form of nodules possibly representing calcified atheromatous patches. The areas which stained blue with hæmatoxylin were tested for calcium, iron, fat and amyloid. By means of Roehl's method the deposit was proved to be calcific, and by means of the hydrochloric acid-potassium ferrocyanide test iron was also shown to be present, a finding which bears on the question of the relation between iron and calcification. (It should be stated that we did not use iron-free re-agents.) There was fat present throughout most of the section, but not particularly much in the calcified areas, so that no relation between the deposit of lime and a previous infiltration of fat was indicated. The test for amyloid proved negative. According to Poscharissky² an important point of resemblance between normal and pathological ossification is the presence of amyloid in the ground substance. The search by means of the orcein stain for elastic tissue in the calcific areas was not successful, probably because of the degenerated condition of the whole inner coat.

As was already stated, we found an ossifying area in the thickened, degenerated calcified endocardial coat of the left auricle. This area consists of a ground substance which stains well with eosin (osteoid ground substance) and of included nucleated elements. These included nucleated elements exhibit some shrinkage, and are surrounded by lacunæ with canaliculi indicated here and there; in brief, their transformation into true bone corpuscles is well under way. A vascular connective tissue lying in bays of the ossifying plaque seems to be invading it and causing

its resorption. Erosion is indicated by the notches of the border of the plaque. Along the crenated border bounding the vascular connective tissue the matrix stains blue with hæmatoxylin-eosin, indicating calcification of the osteoid ground substance to form the matrix of true *bone*. The bays of young connective tissue included in the osseous plate, we consider marrow spaces, and the connective tissue itself primitive marrow. This marrow presents no osteoblasts or megalokaryocytes. It consists of a fine reticulum in the meshes of which are many blood vessels and some blood sinuses, numerous fibroblasts, some polymorphonuclear leucocytes and lymphoid cells, some cells with kidney-shaped nuclei and with eosinophilic granules, some cells which seem to be normoblasts, and not a few polynuclear giant-cells. These last lying in indentations of the ground substance, are evidently osteoclasts. Indeed the osseous plaque seems to be undergoing lacunar resorption not only by means of the osteoclasts but also by means of the rest of the elements of the young vascular connective tissue such as the large blood sinuses, the blood vessels and free blood.

Apparently the osseous elements, inasmuch as they occur in the endocardial coat, were not being formed in connection with normal cartilage or bone-forming structures or from displaced embryonal cartilage or bone "Anlagen."* There are present in the inner coat of the left auricle the two features generally considered essential to bone-formation, namely, young connective tissue and lime. One may account for the presence of young connective tissue and lime as follows: We consider that a lesion, namely, a hyaline degeneration of practically the entire endocardial coat of the left auricle preceded the deposition here and there of lime salts. As to the young connective tissue it may possibly be inflammatory in origin, but it is more likely that the calcareous foreign body as such resulted in a reactive proliferation

*In explaining the presence of bone in such unexpected places as the circulatory system Bunting³ says "one would turn naturally to the Cohnheim doctrine of embryonic displacement of tissue, were not the cases so numerous, and did not the figures just quoted show such a frequency of occurrence of the process in advanced arteriosclerosis."

of vascular connective tissue, which in turn formed a young marrow in concavities of some of the lime plaques.

Though we believe that the deposition of lime was conditioned by the local hyaline degeneration of the cardiac tissue, we must admit the possibility that an increased calcium content of the circulating body fluids *may* account for the lime deposit in the left auricle. We grant this possibility because we were unable to exclude it by an examination of the excretions during life or of the bones post-mortem. Moreover, in this case as in those of Davidsohn,⁴ of Lazarus and Davidsohn⁵ and of Verse,⁶ the calcification is on the left side of the heart; and in these cases of calcium metastases it is deemed likely that the same chemical factors which so often result in calcification of the lung, have resulted in calcification on the left side of the heart in contradistinction to the right.

On the other hand in our case sections of the lung, kidneys, liver and spleen, free of lime as they are, indicate *that calcium metastasis played no role*.

The underlying cause for the hyaline degeneration of the endocardial connective tissue is unknown, nor is it clear in what way this lesion is associated with the auricular fibrillation.

The calcific ossifying plate is within the muscular layer, that is on the lumen side of the auricle, and the muscular layer must have been stretched over it. Under these conditions the muscle would probably be unable to contract down on this firm plate, and would consequently be paralyzed or be thrown into fibrillation. As soon as one auricle fibrillates, the musculature connections between the two are so intimate, that the other is at once thrown into a similar condition of incoördination. This is only an hypothesis of the mechanism by which auricular fibrillation may have arisen in this case.

A gross specimen of the heart and a slide showing an osteogenic area in the calcific plate were presented.

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A PEDUNCULATED CARDIAC POLYP.

B. S. OPPENHEIMER, M.D. AND S. GEORGE EHRENREICH, M.D.

The following is an example of one of those rare, peculiar, solitary, organized thrombi in the heart, which are quite distinct from ordinary cardiac thrombi. It presented histological features which differed somewhat from those which have been described in other instances of similar formations.

The patient from whom the specimen was obtained was a pianist, fifty-three years old, who was admitted to Montefiore Home, March 18, 1912, in good general condition with slight symptoms of a chronic nephritis. On the 26th of March she had a sudden chill lasting over an hour, followed by a rise of temperature. This chill was repeated two days later, March 28. That afternoon she became very drowsy, and within the next few days she developed a complete ophthalmoplegia of the left eye and a right-sided hemiplegia with Cheyne-Stokes respiration. A clinical diagnosis of cerebral embolism was made. Patient went into coma and died next day, March 31. Her death, as in cases of ball-thrombus, was not sudden but gradual.

The physical examination of her heart during life showed a slight enlargement to the left, accentuation of the second aortic sound, impurity of the first sound at the apex, but no murmurs.

The autopsy was performed by Dr. Ewing, to whom we are greatly indebted for the specimen.

The spleen and kidney presented multiple infarcts.

The brain showed a long decolorized clot in the left cerebral artery and partial softening of much of the brain tissue supplied by this vessel.

There was found attached to the posterior inferior border of the foramen ovale and projecting into the cavity of the left auricle, a pedunculated tumor which at that time was the size of a hen's egg (See fig. 1). It had been shrunken by alcohol and reduced in size by having a large section cut out of it. The surface was in parts smooth and shiny, in other parts covered with fibrin, and the cut section exhibited concentric layers. Its pedicle

was short and rather broad, measuring 1.5 cm. in diameter. The left auricle was hypertrophied and dilated; after preservation, its cavity measured 5.5 cm. in length, 4.5 cm. in width, and 4.5 cm. in depth. On the lateral endocardial surface of the left auricle there was a flat, firm, slightly elevated area about 2.5 cm. in length; otherwise the endocardium was smooth. There were no other thrombotic masses to account for embolism. The foramen ovale was not patent. The coronary arteries showed marked sclerosis with numerous calcareous plaques. At the time of the autopsy the pathological diagnosis of the growth rested between a thrombus, and a myxoma or sarcoma.

Microscopic section of the pedunculated tumor reveals a well organized thrombus with old and young connective tissue, blood vessels, pigment cells, some calcareous infiltration and interesting cords of endothelial cells which are interpreted as vascular sprouts.

The tumor springs from the septal wall of the left auricle in a region where the endocardium is thickened and vascularized. At the base of the short stalk there is a round celled infiltration. The pedicle itself consists of a very vascular connective tissue with pigment-bearing phagocytes.

The globular portion of the thrombus can be roughly divided into several areas. Nearest the stalk is a region characterized by long cords of endothelial cells which run transversely and roughly parallel with one another. These cords show a tendency to send off branches more or less at right angles, and in certain places in these branches the cells are arranged lengthwise along a lumen, apparently forming young capillaries. Between the endothelial cords are masses of pigment-cells. (See fig. 2.)

Distal to this region of cords of endothelial cells, the thrombus consists to a much greater extent of cells bearing pigment, which gives the staining reaction of hemosiderin. These phagocytes also give the staining for calcium with Roehl's method and fat with Scharlach R.

In this area and in the one further out there are rods stained deep blue with haematoxylin, which upon further study (with

special stains) proved to be elastic tissue fibres that give positive reactions both for hemosiderin and calcium.

The region distal to the area of pigment-cells, consist of masses of polynuclear leucocytes and round cells.

Beyond this is an area consisting of a matrix with a very few cells, chiefly pigment cells. This matrix is the same as is found throughout the thrombus. It usually takes the eosin stain; sometimes the hæmatoxylin. In most parts it is fibrous in appearance, in other parts it is homogeneous, in still other parts it is flocculent. Staining reactions for mucin and for fibrin proved negative, as is not infrequently the case.

These four regions which consist prevailingly, the first of endothelial cords, the second of pigment-bearing cells, the third of pus cells, and the fourth of an almost non-cellular matrix, are not sharply defined strata. The different kinds of cells mentioned are found in the various parts of the thrombus, and in addition there are fibroblasts, plasma cells, resting-wandering cells and red blood cells. The polyp is not covered with endocardium.

There is as yet no hypothesis which satisfactorily accounts for these polyps but Bostroem's explanation of their origin in thrombosed varices of the interauricular septum seems to apply to at least a few of the cases.

Of the thirty-three cases collected from the entire literature since 1809 by Welch (of which at least twenty were typical instances,) four sprang from the left ventricle, four from the right auricle, and twenty-five from the left auricle, and usually from the septal wall, just as in the case here presented.

Discussion.

DR. EWING: At first I thought this process was a transformed myxoma, but have finally agreed with Dr. Oppenheimer that the condition is a simple pedunculated thrombus.

ILLUSTRATIONS.

FIG. 1.—Heart cut open, from the anterior aspect, showing the pedunculated thrombus in the left auricle.

FIG. 2.—Section from the pedunculated thrombus of the heart, showing a cord of endothelial cells which at one extremity arrange themselves lengthwise along a lumen; showing also the matrix of the thrombus with plasma and round cells and (at the bottom of the drawing) a group of pigment cells; (1) Endothelial cells arranged lengthwise along a lumen; (2) a cord of endothelial cells; (3) a group of pigment cells.



FIG. 1.

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Section from the pedunculated thrombus of the heart, showing a cord of endothelial cells which at one extremity arrange themselves lengthwise along a lumen; showing also the matrix of the thrombus with plasma and round cells and (at the bottom of the drawing) a group of pigment cells.

1—Endothelial cells arranged lengthwise along a lumen

2—A cord of endothelial cells

3—A group of pigment cells



FIG. II.

ENDOTHELIOMA OF LYMPH-NODES.

JAMES EWING, M.D.

Dr. Ewing presented the clinical histories, stained sections, and photographs of a series of cases of endothelial hyperplasia and endothelioma of lymph-nodes, and drew the following conclusion from their study:

General Conclusions.

1. Extreme grades of endothelial hyperplasia are not infrequently associated with and dependent upon granulomatous infection of lymph-nodes, and these cases demonstrate the capacity of endothelium to respond to inflammatory irritation with extensive proliferation.

2. In some cases it is difficult or impossible to determine whether this overgrowth is simply inflammatory or independent of the irritant, autonomous and neoplastic.

3. The long-continued effect of granulomatous infection may lead to neoplastic growth of lymphatic endothelium; in the course of a granulomatous infection of lymph-nodes, after repeated operations, granulomatous elements may apparently be eliminated and the disease progress as a form of neoplasm.

4. Granulomatous infection of lymph-nodes may very early give rise to excessive overgrowth of endothelium of distinctly anaplastic type, and with local aggressive properties.

5. Such malignant endotheliomas may arise without any evidence of an associated granuloma. It is possible to conceive that an original infectious focus may be overgrown and obscured by the neoplastic cells. No definite evidence of such an event has been secured, but it has been shown that one node of a chain may exhibit purely neoplastic overgrowth, while others show chiefly granuloma.

6. Certain endotheliomas of lymph-nodes designated as diffuse plexiform, perivascular, or alveolar, are probably derived from the endothelium of lymph-sinuses and lymph-cords.

7. Certain primary tumors of lymph-nodes, with or without

associated granuloma, are probably derived from the reticulum cells of the follicles. These tumors resemble lymphosarcoma with large cells, and may be distinguished from tumors of small lymphocytes.

8. Endothelioma of lymph-nodes differs from other neoplasms in several particulars, and may be regarded as a disease *sui generis*, although nevertheless essentially neoplastic.

A SERIES OF CASES OF STAPHYLOCOCCUS AUREUS SEPSIS.

WILLARD B. SOPER, M.D.

The following report is based upon a series of cases collected from the records of St. Luke's Hospital, the Roosevelt Hospital and the Presbyterian Hospital. There were in all forty cases, in which the *Staphylococcus Aureus* was found in blood cultures, and which are unquestioned. There were twenty-nine deaths, with eight autopsies; and eleven recoveries.

Summary of lesions diagnosed clinically and at autopsy:

	<i>Cases.</i>	<i>Per Cent.</i>
Osteomyelitis	16	40
Pneumonia	12	30
Suppurative Arthritis	10	25
Cellulitis	10	25
Suppurative Nephritis	6	15
Carbuncle	6	15
Abscesses of Lungs	5	12.5
Suppurative Myocarditis	4	10
Suppurative Meningitis	3	7.5
Splenic Infarctions	3	7.5
Acute Vegetative Endocarditis	2	5
Thrombosis	2	5
Brain Abscess	1	2.5
Abscesses of Spleen	2	5
Perinephritic Abscesses	2	5

Course of Disease:

Of the twenty-nine cases with fatal outcome, twenty cases, or twenty-nine per cent., showed a duration of fifteen days or less after onset. Of the remaining nine cases which died, only three survived one month. The recoveries, as was to be expected, showed a long duration; the shortest six weeks, the longest six months, with the majority about three months.

Conclusion as to Treatment:

There seems to be a fulminant type or rather one in which either the infection is overwhelming or the resistance markedly low. This type is of a frequency about equal to that of the less severe type—in this series the figures standing about twenty to twenty. With this type, which is represented clinically by an excessive toxæmia and a larger number of colonies where blood plates are made, the prognosis is extremely grave. However, the number of recoveries in this series, coupled with the often remarkably rapid disappearance of cocci from the blood following removal of the infective focus, demonstrates that no case is hopeless provided the infective focus can be reached by the surgeon.

Discussion.

DR. E. LIBMAN: In a discussion of Dr. Soper's paper which I gave before the Medical Section of the Academy of Medicine some time ago, I made an error in stating that I had seen 150 cases of staphylococcus aureus general infection. In looking over my records I find that I have 130 odd cases. A number of years ago I read a paper before this society on a study of twenty-three cases.

In children the staphylococcus aureus circulating in the blood has a special predilection to lodge in the bones and that explains the frequency of acute osteomyelitis in children as compared to the same disease in adults.

Dr. Soper has reported a case of general infection in dia-

betes. Such cases in my experience are not very common. It is a curious fact that whenever one has a focus in the body containing carbohydrates it is uncommon to find a general infection. One almost never gets a general infection due to a pylephlebitis, but it is much more frequent in infections of the duct system of the liver.

In staphylococcus infections of the lactating breast I have not seen a single case of general infection in ten years, no matter how severe the clinical picture was.

In staphylococcus infections of the endocardium the cardiac phenomena play very little role, because, as a rule, the cases terminate so rapidly. Often one finds only a small deposit of fibrin on one of the valves or on the endocardium of the ventricle.

General infections in the puerperal period, due to the staphylococcus aureus, are very uncommon. When they do occur the entering point seems to be more in the cervix or vagina, rather than in the uterus.

I have never seen a case of lobar pneumonia due to the staphylococcus. The lesions found in the lungs in cases of general infection by the staphylococcus are rather characteristic and look like hemorrhagic furuncles, the central purulent point often being quite small. There is no great tendency for the staphylococcus to multiply in the blood stream. The chance of recovery depends to a great extent on whether the local foci which are causing the general infection can be dealt with surgically in a satisfactory manner or not.

When the staphylococcus albus is found in the blood in large numbers and no primary inflammatory focus can be found, the prognosis is usually exceedingly bad. In such cases the staphylococci have evidently entered from the intestine or other mucous membranes or from the skin and multiply in the blood because the patient has no resistance.

DR. MACCALLUM: I was once very much impressed by a case of staphylococcus albus infection in which the focus of infection was from a very slight scratch of the skin.

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